

Auditory Discrimination After Left-Hemisphere Stroke

A Mismatch Negativity Follow-Up Study

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Background and Purpose—We sought to determine the recovery of cortical auditory discrimination in aphasic, left-hemisphere-stroke patients by using an electrophysiological response called mismatch negativity (MMN) and speech-comprehension tests.

Methods—MMN in 8 left-hemisphere stroke patients was recorded in response to duration and frequency changes in a repetitive, harmonically rich tone 4 and 10 days and again 3 and 6 months after their first unilateral stroke. Eight age-matched, healthy persons served as control subjects.

Results—At 4 days after stroke onset, patients' sound discrimination was impaired in their left hemisphere, as suggested by attenuated MMNs, especially to right-ear stimuli. At 3 months after stroke, however, MMN to the right-ear duration change had significantly increased and was of normal size. A significant change for the frequency MMN was found for left-ear stimuli between 3 and 6 months after stroke. During the follow-up period, progressive improvement in speech-comprehension tests was also observed. Furthermore, there was a significant correlation between the change in the duration MMN amplitude and the Boston Diagnostic Aphasia Examination speech-comprehension test from 10 days to 3 months after stroke.

Conclusions—These results suggest that the MMN can be used as an index of the recovery of auditory discrimination. (*Stroke*. 2003;34:1746-1753.)

Key Words: aphasia ■ hearing disorders ■ laterality ■ mismatch negativity ■ speech ■ stroke outcome

The processes underlying the recovery from a brain stroke have been widely studied with functional neuroimaging methods, such as positron emission tomography, single-photon emission computed tomography, and functional magnetic resonance imaging (MRI). Although these technologies reveal accurate information on the loci of the activated areas, they lack good time resolution. In contrast, in the case of strokes that affect central auditory processing, the neural basis of sound discrimination can be studied with millisecond temporal accuracy with an event-related-potential (ERP) component called mismatch negativity (MMN).

MMN is elicited by occasional changes in repetitive, auditory stimulation.¹ The repetitive, "standard" stimuli form a memory trace with which each incoming stimulus is automatically compared. If a stimulus does not match with this trace, an MMN is elicited, peaking at 100 to 250 ms from the onset of the deviant stimulus. This comparison process provides information about sound-discrimination accuracy.¹ MMN is elicited by any discriminable change in homogeneous auditory stimulation,² and it is correlated with the

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accuracy of behavioral discrimination of sound changes.^{3,4} MMN is generated in the auditory and frontal cortices.⁵⁻⁷

Although attention may have some effect on MMN amplitude,⁸ it is elicited even when the subject is not attending to auditory stimuli¹ and thus, can be used for determining auditory discrimination accuracy in inattentive patients. For example, Deouell et al⁹ used MMN to study the discrimination of different sound features in patients with right-hemisphere damage that caused a neglect to the left hemifield. These investigators found diminished MMNs for location but not frequency or duration changes in sounds presented in the neglected hemifield. Hence, MMN results suggested a specific, low-level, location-processing deficit that presumably accounted for the impaired attention-switching mechanism in the neglect patients (see also Alho et al⁷ for attention-switching and MMN in patients with frontal-lobe damage). MMN has proven useful also in studying other patient groups who have problems in attending stimuli,

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TABLE 1. Demographic Characteristics and Clinical Findings of the 8 Stroke Patients

Patient, Sex, Age	Measurement Time	BDAE Rate of Aphasia	BDAE Percentiles (4 Subtests)	Token Test	Aphasia Type	CT and MRI Findings
1, F, 55	10 d	1	20	3/36	Global	FTA
	3 mo	1	6.3	...	Global	
	6 mo	1	37.5	7/36	Transcortical sensory	
2, M, 63	10 d	0	Global	FTA
	3 mo	1	
	6 mo	3	51.3	...	Transcortical sensory	
3, M, 43	10 d	2	...	32/36	Conduction	FTPA
	3 mo	3	77.5	35/36	Conduction	
	6 mo	4	85.5	35/36	Conduction	
4, M, 50	10 d	1	67.5	12/36	Conduction	FTPA
	3 mo	2	85	27/36	Conduction	
	6 mo	3	87.5	27/36	Conduction	
5, M, 55	10 d	1	68.7	13/36	Conduction	FTPA
	3 mo	3	80	24/36	Conduction	
	6 mo	3	80	31/36	Conduction	
6, M, 62	10 d	0	0	0/36	Global	FTPA
	3 mo	1	23.7	1/36	Global	
	6 mo	1	32.5	11/36	Global	
7, M, 54	10 d	1	25	7/36	Wernicke	FTPA
	3 mo	3	73.7	25/36	Wernicke	
	6 mo	4	77.5	29/36	Wernicke	
8, M, 59	10 d	2	67.5	25/36	Wernicke	FTPA
	3 mo	4	80	32/36	Anomic	
	6 mo	5	87.5	30/36	Anomic	

BDAE indicates Boston Diagnostic Aphasia Examination. The rate of aphasia was evaluated with a scale from 0 to 5 in BDAE. FTA, frontotemporal area; FTPA, frontotemporoparietal area.

understanding instructions, or carrying out behavioral tasks, eg, comatose, locked-in, or aphasic patients (for a review, see Näätänen and Escera¹⁰). Moreover, MMN can also be used for determining cortical plastic changes caused by training or remediation programs.^{11,12} Although MMN has mainly been used for demonstrating group differences, it is reliably elicited especially by sound-duration decrements even at the individual level.^{13,14}

Aphasia, caused by lesions in the left temporoparietal and frontotemporoparietal regions, impairs patients' performance in tasks requiring the discrimination and sequencing of verbal and nonverbal acoustic stimuli.¹⁵ Until recently, most of the evidence on deficits in auditory discrimination in such left-hemisphere-lesion patients has been obtained by using behavioral paradigms,¹⁶ which do not permit one to unequivocally determine whether the deficit involves preattentive auditory discrimination or later processing stages. Some recent studies used MMN to determine auditory processing dysfunction in patients with temporal-lobe lesions.¹⁷⁻²⁰ MMN indicated impaired automatic sound discrimination that showed, for example, the effects of lesion locus on the discrimination dysfunction.¹⁸ Furthermore, auditory discrimination deficits in the left versus right temporal lobe can in some cases be more precisely determined with MMN than by using behavioral means.²⁰ For instance, in left-hemisphere-stroke pa-

tients, the MMN to left-ear stimuli was almost of normal size over the right hemisphere, whereas the MMN to right-ear stimuli was diminished over the left hemisphere.²⁰ However, the patients' behavioral target discrimination was generally poor, there being no ear effect on performance. Thus, these results encourage the use of MMN in determining sound-discrimination abilities in patients who have problems in carrying out behavioral tasks.

In the present study, MMN to duration and frequency changes was measured in 4 different sessions after left-hemisphere stroke to determine the time course of the spontaneous recovery of auditory discrimination functions. In addition, changes in the clinical status of the aphasia were evaluated with standardized language tests.

Subjects and Methods

The study was approved by the Ethics Committee of the Department of Neurology of the Helsinki University Central Hospital. Informed consent was obtained from the subjects.

Subjects

Eight left-hemisphere-stroke patients (range, 43 to 63 years; mean, 55 years; 1 female) who had had their first-ever brain infarction in the area of the middle cerebral artery participated in the study (for clinical characteristics, see Table 1). The patients had no dementia or previous history of psychiatric disease in their medical history. Brain

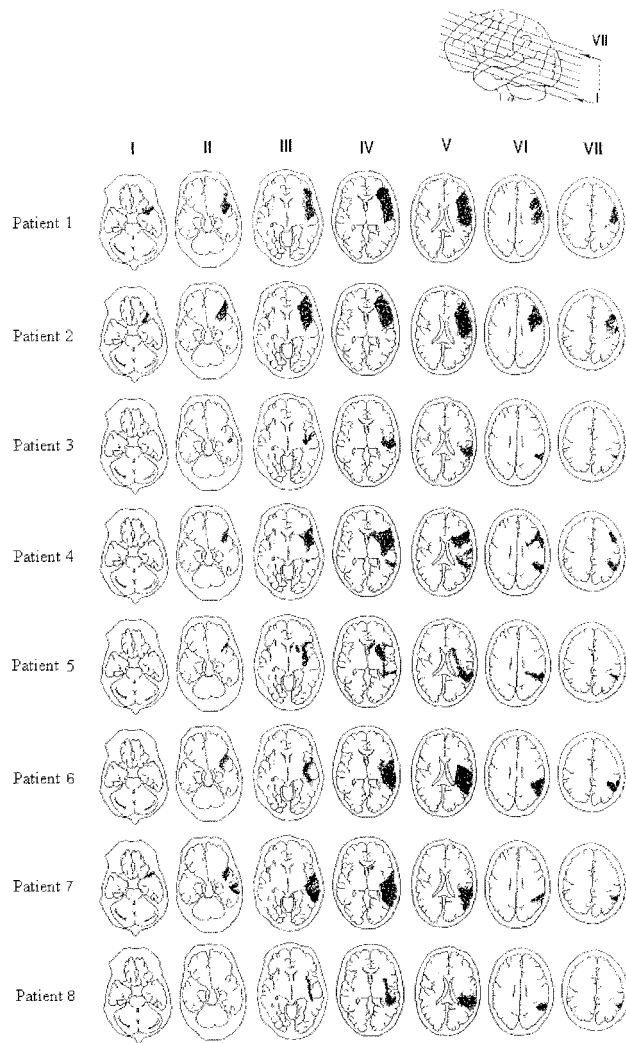


Figure 1. Individual lesion locations determined by CT scans (acute stage) and MRI scans (6 months after stroke). Lines from I to VII through the lateral MRI reconstruction indicate the 7 axial sections shown for each patient. Left and right are inverted.

infarcts were determined by using the acute-stage computed tomography scans routinely acquired during the first day of the patient's hospitalization and the MRI scans obtained 6 months after stroke (Figure 1). All patients in the acute stage had speech-comprehension problems, although they were conscious and relatively alert. Control data were recorded in 8 healthy age- and sex-matched subjects (43 to 63 years; mean, 53 years; 1 female). All patients and control subjects were right-handed. Their hearing was tested with an automatic audiometer (Oscilla SM 950, Oriola; from patients during the 6-month evaluation). The data for 1 patient could not be used because of technical problems. No significant group differences were found in the hearing test. The patients reported having no hearing problem before the stroke.

Stimulation

Stimuli were obtained, with slight modifications, from the paradigms developed in previous studies.^{14,21} Harmonically rich tones consisted of 3 frequency components (500, 1000, and 1500 Hz) with the second and third components being 3 and 6 dB lower in intensity, respectively, than the first component. Four blocks of 1700 stimuli (7.5 minutes each) with a stimulus-onset asynchrony of 300 ms were monaurally presented through headphones to the subjects' left and

right ears in separate sessions. The duration of the standard tone, presented with the probability of occurrence of 0.84, was 75 ms (with 5-ms rise and fall times). There were 2 deviant tones, one of a shorter duration (25 ms; $P=0.08$) and the other of higher frequency (including 575-, 1150-, and 1725-Hz components; $P=0.08$).

Procedure

MMNs elicited by tone duration and frequency changes were recorded in 4 different sessions: 4 days (3 to 5 days; mean, 3.6 days), 10 days (9 to 10 days; mean, 9.8 days), 3 months (60 to 101 days; mean, 90.5 days), and 6 months (165 to 207 days; mean, 182 days) after stroke onset. During MMN recordings, subjects were instructed to watch a silent video and ignore the tones.

Data Acquisition

The nose-referenced electroencephalogram (EEG; filtered with a bandpass of 0.1 to 100 Hz and sampled with 250 Hz) was recorded from 9 scalp sites (F3, Fz, F4, C3, Cz, C4, P3, Pz, and P4) of the 10-20 system as well as from the left and right mastoids and averaged off-line. Horizontal and vertical eye movements were monitored with electro-oculogram (EOG) electrodes attached to the left outer canthus and above the left eye.

The analysis period was 350 ms, including a 50-ms, 0- μ V prestimulus period. All epochs with voltage variation exceeding 100 μ V in any of the EOG or EEG electrodes were omitted. The nose-referenced ERP data were filtered with a passband of 1 to 12 Hz²² and re-referenced to the average of the left and right mastoids before MMN analyses.²³ MMN amplitude and latency values were determined from the difference waves obtained by subtracting ERPs to standard tones from those to deviant tones. MMN was identified as the largest negative peak between 100 to 300 ms at Fz. For the amplitude analyses, the grand mean latencies were determined. Thereafter, the amplitude values were measured from individual difference waves with a 30-ms window centered at the grand mean latency. The data for patient 2 in the first measurement could not be used because of technical problems during the EEG recording. The data from patients 3 and 6 could not be measured at 10 days after stroke, because they were moved to another hospital.

Statistical Analyses

Student's 2-tailed t test was used to determine the significance of MMN in comparison with 0 μ V. The amplitude and latency differences between the groups and within the patient group between sessions were compared with ANOVAs. Electrodes F3, Fz, and F4, where the MMN is largest,⁵ were included in the analyses. Greenhouse-Geisser corrections were applied when appropriate.

Speech-Comprehension Tests

The auditory subtests (word discrimination, body-part identification, commands, and complex ideational material) from the Boston Diagnostic Aphasia Examination (BDAE, standardized for the Finnish language²⁴) and the shortened form of the Token test²⁵ constituted the measures of linguistic auditory performance (see Table 1). To classify the patient's type of language impairment, the BDAE Aphasia Severity Rating scale was used. The patients were tested by a speech pathologist at 10 days, 3 months, and 6 months after stroke onset. The correlations between MMN amplitude changes and the changes in the aphasia tests were studied with Spearman rank-order correlations.

Results

MMN Significance

Figure 2 shows the grand mean MMN waves. MMN mean amplitudes and latencies and the results of t tests that compared MMN amplitudes to zero level are presented in Table 2. MMN amplitude significantly differed from the zero level in all frontal channels for each stimulus type and ear of stimulation in the control group. The main findings in the

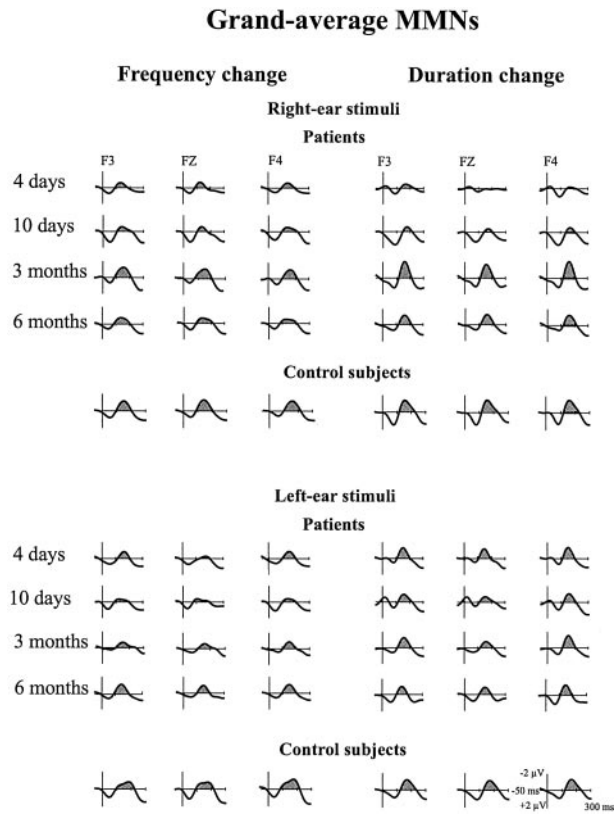


Figure 2. Grand mean MMNs (shaded areas) calculated by subtracting ERPs elicited by standard tones from those elicited by deviant tones.

patients were the nonsignificant MMNs for all deviant types 10 days after stroke and significant MMNs for all deviant types 3 months after stroke.

Group Comparisons

At the 4-day measurement, a significant group-by-ear interaction was found for MMN amplitude [F(1,13)=5.7, *P*<0.05; analyses including levels group, ear, stimulus type, and electrode). Separate analyses for left- and right-ear stimuli showed a significant MMN amplitude attenuation in the patient group for the right-ear duration change [F(1,13)=5.06, *P*<0.05, 2-way ANOVA].

The patients had a significantly shorter latency than did controls for the left-ear duration change [Fz: F(1,13)=10.2, *P*<0.01; F4: F(1,5)=5.3, *P*<0.05] 4 days after stroke onset. However, at 6 months, MMN latency was significantly shorter in the control than in the patient group for the right-ear frequency change [F4: F(1,14)=5.07, *P*<0.05; Fig 2].

MMN Changes in Patients Throughout the Sessions

When all 4 sessions were included in the analysis, a significant amplitude main effect for the right-ear duration MMN was found [F(3,12)=3.8, *P*<0.05; 2-way ANOVA; levels for session and electrode). Post hoc least significant difference (LSD) analyses revealed a significantly larger MMN at 3 months than at any other session (*P*<0.05).

Pairwise comparisons of the sessions indicated that MMN amplitude was significantly larger at 3 months than at 10 days for the right-ear duration change [F(1,5)=16.26, *P*<0.01; 2-way ANOVA; levels for session and electrode]. In addition, it was significantly larger at 6 than at 3 months for the left-ear frequency change [F(1,7)=7.85, *P*<0.05; 2-way ANOVA; levels for session and electrode).

Speech-Comprehension Tests

In the Token test scores for the 3 latest sessions (10 days, 3 months, and 6 months), a significant session effect [F(2,10)=12.13, *P*<0.01; 1-way ANOVA) was found, as a result of significantly better performance at 6 months than at the other sessions (post hoc LSD test, *P*<0.001; Figure 3b). Further analyses revealed that the scores were significantly higher at 3 and 6 months than at 10 days after stroke onset [F(1,5)=11.21, *P*<0.05; F(1,6)=15.57, *P*<0.001; 1-way ANOVA).

In the percentiles of the BDAE, a significant session effect was found [F(2,10)=8.01, *P*<0.01; 1-way ANOVA), resulting from a significantly higher percentile at 6 months than at the other sessions (post hoc LSD test, *P*<0.01; Figure 3a). Further analyses revealed a significantly higher percentile at 6 months than at 10 days [F(1,5)=17.85, *P*<0.01; 1-way ANOVA).

There was a significant correlation between the changes in BDAE percentiles and MMN amplitudes for the right-ear (*r*=0.9, *P*<0.05) and left-ear (*r*=0.9, *P*<0.05) duration changes from the 10-day to the 3-month measurements. There were no correlations between Token test scores and MMNs.

Discussion

The main finding of the present study was the amplitude enhancement of MMN during recovery from left-hemisphere stroke, in parallel with the improvement in speech-comprehension tests. These results suggest that the MMN reflects recovery from the brain dysfunction caused by stroke and dynamic, plastic changes in the cortical substrate of auditory discrimination.

Approximately 4 days after stroke, patients had an attenuated MMN to the right-ear duration change. This might have been caused by overall metabolic depression and ischemic brain edema, which start within the first days after stroke, with maximal swelling on days 3 to 5, which dampens neural processes and affects overall EEG activity.²⁶ Furthermore, edema might also spread outside the primary injury area, thus involving increasing volumes of brain tissue and causing, eg, intracranial swelling and neuronal death.²⁶ In addition to direct cell death caused by ischemia, glutamate excitotoxicity after stroke might also result in neuron damage in stroke patients.²⁷ Pharmacologic studies have demonstrated that MMN is under glutaminergic modulation.²⁸ Hence, increased glutaminergic activity after stroke might have contributed to the observed MMN changes in the present study. Interestingly, 10 days after stroke onset, MMN was still abnormal for both stimulus types, irrespective of the stimulated ear. This might have been caused by the coinciding effects of reduced metabolism and blood flow in the infarcted area

TABLE 2. Mean Amplitudes and Latencies of MMN Elicited by Duration and Frequency Changes Over the Left Hemisphere (F3), Midline (Fz), and Right Hemisphere (F4) in Patients and Control Subjects

	Left-Ear Stimuli						Right-Ear Stimuli					
	Duration			Frequency			Duration			Frequency		
	F3	FZ	F4	F3	FZ	F4	F3	FZ	F4	F3	FZ	F4
Amplitude, μV												
4 d	-1.2*	-1.1*	-1.2*	-1.2*	-0.5	-1.2*	-0.6	-0.1	-0.4	-0.6*	-0.7**	-0.5
10 d	-0.9	-0.6	-1.0	-0.4	-0.4	-0.3	-0.6	-0.4	-0.5	-0.5	-0.6	-0.6
3 mo	-1.3**	-0.9*	-1.5**	-0.6*	-0.6*	-0.8*	-1.9*	-1.5*	-1.9*	-1.0*	-1.0	-1.0*
6 mo	-1.0*	-0.8*	-1.2**	-1.1**	-0.9**	-1.1**	-1.2**	-1.4*	-1.3**	-0.7	-0.7	-0.5
Latency, ms												
4 d	174	142	144	161	155	140	197	187	195	145	133	153
10 d	177	168	156	165	163	184	186	203	182	168	158	170
3 mo	162	169	162	155	161	156	151	176	152	176	145	168
6 mo	154	153	153	143	141	146	150	160	169	145	150	142
Controls												
Amplitude, μV	-1.2**	-1.1**	-1.2**	-0.8**	-0.8**	-1.0**	-1.4**	-1.4**	-1.3**	-1.1**	-1.3**	-1.1**
Latency, ms	182	183	182	154	150	158	163	156	157	140	136	138

* $P < 0.05$, ** $P < 0.01$ (2-tailed t test for dependent samples).

and the diaschisis in the contralateral hemisphere, with abnormalities in the glutaminergic transmitter system.²⁷

A dramatic MMN amplitude increase for the right-ear duration change was seen at 3 months after stroke. These results are in agreement with positron emission tomography and functional MRI studies, which have shown that 3 months after left-hemisphere stroke onset, there is increased metabolic activity in the left hemisphere.^{29,30} Corroborating results have been provided by several EEG^{31–33} and behavioral^{34–36} studies that showed enhancement in electrical activity and recovery of language functions during 3 months after left-hemisphere stroke.

MMN amplitude for the left-ear frequency change was significantly larger at 6 than at 3 months. Given that left-ear

stimulation primarily activates the right hemisphere, these results suggest changes in the right hemisphere between 3 and 6 months. This is consistent with previous studies that have indicated a contralateral-hemisphere contribution to recovery from the effects of brain lesions.³⁷ The duration and frequency MMNs had different recovery times (amplitude increase by 3 and 6 months after stroke, respectively). Furthermore, the significant amplitude changes were found for the right-ear stimuli in duration MMN and for the left-ear stimuli in frequency MMN. These results suggest, consistently with previous studies in healthy subjects,^{5,6} different MMN generators for different deviant types.

The results of the language tests showed a significant increase in Token test scores from 10 days to 3 and 6 months and in BDAE percentiles from 10 days to 6 months. Several previous studies with various language tests also suggest that the recovery of language functions is the most rapid during 3 months after stroke.^{33–36} The most dramatic MMN amplitude changes also occurred by the 3-month measurement. Furthermore, there was a significant correlation between the changes in BDAE percentiles and the duration MMN amplitudes from the 10-day to the 3 months measurement. Thus, MMN amplitude increased with the improvement in speech comprehension.

The present results promote the usefulness of MMN in studying brain dysfunction and recovery. As also evident in this study, early diagnosis with neuropsychological tests can be problematic for several days after stroke, whereas the MMN paradigm could be successfully applied even within a few days after stroke onset. Furthermore, the pattern of recovery indicated by the MMN results was in agreement with the speech-comprehension tests. In future work, it would

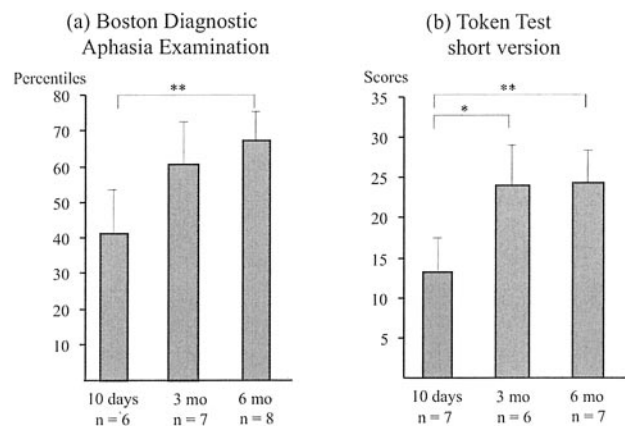


Figure 3. Percentiles of the BDAE (a) and test scores of the Token test (b), with mean and SEM. Significance of difference in test points between measurement times is marked with asterisks: * $P < 0.05$, ** $P < 0.01$ (1-way ANOVA).

be important to establish with a larger patient cohort how strongly MMN is correlated with speech-perception measures and also to determine the optimal stimulus parameters for acquiring the MMN that has the strongest correlations with speech-comprehension tests. This might give a means to assess the functional state of the cortex, even before the patient is able to carry out any speech-comprehension test. Especially in patients with severe aphasic syndromes and a multitude of communication problems, this approach might provide valuable information on their sound and speech perception.

In summary, MMN appears to reflect the recovery of sound discrimination from stroke and occurs in parallel with alleviation of the aphasic symptoms. At the acute stage, MMN was diminished in amplitude, especially for right-ear stimulation. Three months after stroke, by which time the most active, spontaneous recovery should occur,^{33–36} MMN had dramatically increased, especially for the right-ear duration change.

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Editorial Comment

Implementing Results of Stroke Recovery Research Into Clinical Practice

Most patients show some recovery of deficits in the weeks-months following a focal infarct. Numerous studies have characterized the molecular, cellular, systems, and behavioral level¹⁻³ brain changes related to this recovery. In the current article, Ilvonen et al,⁴ using mismatch negativity (MMN), describe an evolution of brain physiology that paralleled recovery of language. Consistent with prior studies using functional MRI (fMRI)⁵ or positron emission tomography (PET),⁶ these authors found changes in brain function within both hemispheres as language improved. Apart from new information on brain reorganization gained from this investigation, this report has significance in at least 2 other ways: only passive patient participation was needed to probe the brain, and the methods employed can be easily implemented in thousands of medical facilities worldwide.

MMN is a type of auditory-evoked potential that reflects cerebral processing of changes in the acoustic environment. An auditory stimulus is presented while scalp electrodes record cortical potentials. A change in the auditory stimulus pattern is then introduced, which results in a negative deflection over characteristic brain areas such as frontal or temporal lobes. This deflection represents an objective measure of auditory and language processing that can be elicited in the absence of attention.^{7,8} MMN has provided insights into brain function in a number of brain states,⁹ including conditions in which studying brain physiology can be otherwise difficult, such as schizophrenia¹⁰ and sleep.¹¹

Most methods used to map brain function demand cooperation from the patient being examined. Thus fMRI, PET, and transcranial magnetic stimulation (TMS) study paradigms require patients to actively perform a behavior on cue. The need for such active participation narrows entry criteria (a patient who cannot do the required behavior on command cannot be in the study), and also allows an influence on results by effort, fatigue, attention, cooperation, comprehension, strategy, and other variables. Even in healthy subjects, these variables can have a substantial effect on brain mapping results. For example, shifting the direction of gaze by 20° to 30° during right finger movements modulates the volume of activation in left primary motor cortex by >50%.¹² The MMN brain mapping approach employed by Ilvonen et al⁴ is limited in several regards, such as spatial resolution. The authors do not provide measures of intersubject variance. Also, additional studies are needed regarding the reliability of this method in various stroke populations. Nevertheless, application of MMN to patients with an evolving neurological deficit is of particular value because this means of probing brain function is little influenced by behavioral variables such as attention.^{7,8}

A broad range of molecular, cellular, physiotherapy, and other treatments that target restorative brain events are being developed to improve outcome after stroke. Will these be administered in a one-size-fits-all approach, as with aspirin after stroke? More likely, therapy will be individualized on the basis of clinical data plus a measure of the physiological target, as has been suggested when selecting patients for revascularization or for acute neuroprotective therapies. Examples of this approach in other clinical practice settings include thyroxine dose based on serum assessment of pituitary function and cardiac anti-arrhythmia medication selection based on electrophysiological laboratory studies.

Brain mapping studies employing fMRI, PET, or TMS continue to provide new insights into how the brain changes function in relation to neurological gains after stroke. However, it is unlikely that such methods will enjoy broad application in general neurological practice. If recovery-related processes are to be measured in order to best implement future restorative therapies, what techniques will be used?

Evoked potentials can currently be obtained in hospitals around the world and have demonstrated clinical utility in even complex medical settings. For example, the absence of somatosensory-evoked potentials virtually ensures that a patient with hypoxic-ischemic coma will not awaken.¹³ Evoked responses have been previously used to study stroke recovery; however, the study by Ilvonen et al⁴ is important by virtue of the number of physiological assessments over time and inclusion of a valid behavioral measure. While a range of investigative methods continue to be needed for a better understanding of brain reformatting after stroke, a parallel need exists to characterize accessible methods such as MMN that might be used to reliably measure restorative events in the day to day treatment of individual patients. The MMN study by Ilvonen et al,⁴ in addition to further characterizing return of language function after stroke, is an important step toward this goal.

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