Music and Speech Listening Enhance the Recovery of Early Sensory Processing after Stroke

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Abstract

■ Our surrounding auditory environment has a dramatic influence on the development of basic auditory and cognitive skills, but little is known about how it influences the recovery of these skills after neural damage. Here, we studied the long-term effects of daily music and speech listening on auditory sensory memory after middle cerebral artery (MCA) stroke. In the acute recovery phase, 60 patients who had middle cerebral artery stroke were randomly assigned to a music listening group, an audio book listening group, or a control group. Auditory sensory memory, as indexed by the magnetic MMN (MMNm) response to changes in sound frequency and duration, was measured 1 week (baseline), 3 months, and 6 months after the stroke with whole-head magnetoencephalography recordings. Fifty-four patients completed the study. Results showed that the amplitude of the frequency MMNm increased significantly more in both music and audio book groups than in the control group during the 6-month poststroke period. In contrast, the duration MMNm amplitude increased more in the audio book group than in the other groups. Moreover, changes in the frequency MMNm amplitude correlated significantly with the behavioral improvement of verbal memory and focused attention induced by music listening. These findings demonstrate that merely listening to music and speech after neural damage can induce long-term plastic changes in early sensory processing, which, in turn, may facilitate the recovery of higher cognitive functions. The neural mechanisms potentially underlying this effect are discussed. ■

INTRODUCTION

Our everyday acoustic environment is filled with sounds coming from multiple sources and containing overlapping acoustic properties. For the brain, making sense of this chaotic environment is a highly complex task requiring encoding, storing, and monitoring vast amounts of auditory information. Auditory sensory (echoic) memory is an accurate memory representation of the auditory environment that lasts for several seconds and represents one of the first steps in gating incoming auditory information to the memory system (Cowan, 1988). It is vital for speech comprehension and working memory tasks where relevant auditory information needs to be accessed over a period of a few seconds (Jääskeläinen, Ahveninen, Belliveau, Raij, & Sams, 2007). Functioning of the auditory sensory memory is indexed by a change-specific ERP component called MMN (Kujala, Tervaniemi, & Schröger, 2007; Näätänen, Paavilainen, Rinne, & Alho, 2007). MMN is an early response to a violation of an auditory regularity, such as an infrequent change in the acoustical feature of a repetitive sound, typically peaking about 100–200 msec from the onset of the violation. MMN is elicited even when the subject is not attending to the stimuli (Näätänen, 1991; Alho, Sams, Paavilainen, Reinikainen, & Näätänen, 1989), corresponds well to behavioral sound discrimination accuracy (Novitski, Tervaniemi, Huotilainen, & Näätänen, 2004; Amenedo & Escera, 2000; Jaramillo, Paavilainen, & Näätänen, 2000; Tiitinen, May, Reinikainen, & Näätänen, 1994), and has good test–retest reliability (Tervaniemi et al., 1999, 2005). Thus, it is well suited for studying early auditory processing in clinical patient groups such as stroke patients (e.g., Ilvonen et al., 2003; Csépe, Osman-Sági, Molnár, & Gósy, 2001; Deouell, Bentin, & Soroker, 2000).

Environmental stimuli play an important role in shaping our brain. Evidence from animal studies indicates that an enriched environment can induce plastic changes ranging from biochemical parameters to dendritic arborization, gliogenesis, neurogenesis, and improved learning (van Praag, Kempermann, & Gage, 2000). In the auditory domain, frequent exposure to complex sounds, such as music, not only increases evoked potentials (Engineer et al., 2004) and gating (Percaccio et al., 2005) in the auditory cortex (AC) but can also enhance learning, memory, and neuronal plasticity in the animal brain (Angelucci, Fiore, et al., 2007; Angelucci, Ricci, Padua, Sabino, &

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Tonali, 2007; Nichols et al., 2007; Xu, Cai, Xu, Zhang, & Sun, 2007; Chikahisa et al., 2006; Kim et al., 2006). Similarly, multimodal sensory stimulation, which includes also sound stimuli, has been shown to reduce lesion volume and to improve cognitive and motor recovery after brain injury in rats (Maegele, Lippert-Gruener, Ester-Bode, Garbe, et al., 2005; Maegele, Lippert-Gruener, Ester-Bode, Sauerland, et al., 2005). Collectively, this evidence from animal studies indicates that an enriched sound environment may enhance brain plasticity at multiple levels, influencing both auditory functions and more general learning and memory mechanisms. In humans, the potential therapeutic effect of complex auditory stimuli, such as music and speech, on recovery from neural damage has, however, been largely unexplored.

Previously, we performed a single-blind, randomized, and controlled study to test whether daily music and audio book listening during the early recovery phase after middle cerebral artery (MCA) stroke could improve cognitive recovery and mood. Using an extensive neuropsychological test battery and mood questionnaires, we found that music listening improved verbal memory and focused attention recovery more than audio book listening or non-listening and also prevented depressed and confused mood more than non-listening (Särkämö et al., 2008). The aim of the present magnetoencephalographic (MEG) study was to extend this research into the auditory domain by testing whether music and audio book listening could also influence auditory sensory memory, as indexed by the magnetic MMN (MMNm) response. Moreover, because the patient sample was the same as in our previous behavioral study, we were also interested in finding out whether there is a relationship between the changes in MMNm and the improved cognitive recovery induced by music, suggesting that enhancement of early sensory processing might facilitate the recovery of higher cognitive functions.

METHODS

Subjects and Procedure

Subjects ($n = 60$) were stroke patients recruited between March 2004 and May 2006 from the Department of Neurology of the Helsinki University Central Hospital (HUCH). All subjects had been admitted to the hospital for treatment of an acute ischemic MCA stroke in the left or right temporal, frontal, parietal, or subcortical brain regions. The following additional inclusion criteria were also used: no prior neurological or psychiatric disease; no drug or alcohol abuse; no hearing deficit; right-handed; ≤75 years old; Finnish speaking; and able to cooperate. The patients were randomly assigned to one of three groups ($n = 20$ in each): a music group, an audio book group, or a control group. Randomization was performed with a random number generator by a researcher not involved in the patient enrollment. The study was approved by the HUCH Ethics Committee, and all patients signed an informed consent. All patients received standard treatment for stroke in terms of medical care and rehabilitation. All patients underwent an MEG measurement and neuropsychological testing 1 week (baseline), 3 months, and 6 months after the stroke. In addition, the stroke diagnosis and the location and size of the lesion were evaluated from magnetic resonance images (MRI) taken within 2 weeks of stroke onset and 6 months poststroke with the 1.5-T Siemens Vision scanner of the HUCH Department of Radiology (for details, see Särkämö et al., 2008).

Of the 60 subjects originally recruited into the study, 55 completed the study up to the 3-month follow-up and 54 up to the 6-month follow-up (for group sample sizes, see Table 1). As reported previously (Särkämö et al., 2008, see Tables 1 and 2), there were no statistically significant differences between the music, the audio book, and the control groups in demographical variables (age, gender, education level, music/radio listening or reading prior to stroke), clinical variables (time from stroke; motor deficit severity; presence of aphasia or visual neglect; lesion laterality, location, and overall size; antidepressant medication), mood, or performance on neuropsychological tests at baseline.

Interventions

As soon as possible after hospitalization (3–21 days; mean = 8.6 days), all patients were contacted by a music therapist who interviewed them about their prestroke leisure activities and hobbies, such as music listening and reading, and informed them about the group allocation. In the music group, the therapist provided the patients with portable CD players and CDs of their own favorite music in any musical genre. Similarly, the therapist provided the audio book group with portable cassette players and narrated audio books on cassette selected by the patients from a collection of the Finnish Celia library for the visually impaired (http://www.celia.fi). The control group was not given any listening material. Patients in the music and audio book groups were trained in using the players and were instructed to listen to the material by themselves daily (minimum 1 hour per day) for the following 2 months while

Table 1. Group Sample Sizes at Follow-ups

	LHD		*RHD*		*Total*	
Group	*3 m*	*6 m*	*3 m*	*6 m*	*3 m*	*6 m*
Music	10	9	9	9	19	18
Audio book	8	8	11	11	19	19
Control	8	8	9	9	17	17
Total	26	25	29	29	55	54

Dropouts were due to a false diagnosis (1), new stroke (1), dementia (1), refusal (2), and death (1). LHD = left hemisphere damage; RHD = right hemisphere damage; 3 m = 3-month poststroke stage; 6 m = 6-month poststroke stage.

Table 2. MMNm Amplitudes (nAm) 1 Week Poststroke

		Music Group		*Audio Book Group*		*Control Group*	
Deviant	*Hemisphere*	*LHD (n = 10)*	*RHD (n = 9)*	*LHD (n = 8)*	*RHD (n = 11)*	*LHD (n = 8)*	*RHD (n = 9)*
Frequency	Left	2.6 (1.3)	3.7 (2.1)	2.0 (0.9)	2.9 (2.5)	2.9 (2.4)	2.3 (1.0)
	Right	2.5 (1.2)	1.8 (1.0)	2.7 (2.0)	3.5 (2.8)	3.5 (2.2)	2.4 (1.3)
Duration	Left	6.1 (3.6)	6.2 (4.7)	4.2 (3.2)	5.9 (3.8)	5.0 (2.9)	5.7 (3.4)
	Right	8.5 (5.1)	5.3 (3.2)	8.1 (5.8)	5.1 (4.6)	6.5 (2.2)	5.9 (3.9)

Data shown as mean (*SD*).

still in the hospital or at home. During this time, the music therapist kept close weekly contact with the patients to encourage listening and to provide more material and practical aid. After that, the patients could continue listening to the material on their own. Patient participation was verified from listening diaries, which the music and audio book groups kept during the intervention period, and from questionnaires on leisure activities, including music and audio book listening, which all patients filled after the intervention period and at the 6-month follow-up. In addition, emotional responses and preference to music and speech material were assessed by the therapist before the intervention using a short listening experiment (for details, see Särkämö et al., 2008).

As reported previously (Särkämö et al., 2008), results of the short listening experiment showed that the emotional response to and preference for music and speech material were comparable between the music and the audio book groups at baseline. Furthermore, the three groups received similar amounts of rehabilitation (physical therapy, occupational therapy, speech therapy, and neuropsychological rehabilitation) in public health care during the 6-month follow-up period (see Table 3 of Särkämö et al., 2008). In contrast, results of the leisure activity questionnaires showed that the music group listened to music tapes more than the audio book and control groups, whereas the audio book group listened to audio books more than the music and control groups during the 6-month follow-up period. These results attest that the study protocol worked well.

MEG Measurements

MEG was recorded in a magnetically shielded room (Euroshield Ltd., Eura, Finland) at the BioMag laboratory (HUCH) with a 306-channel whole-head magnetometer (Elekta Neuromag Oy, Helsinki, Finland), which has 102 three-sensor units, each comprising two gradiometers and a magnetometer. The position of the subject's head relative to the sensors was determined by measuring the magnetic field produced by four marker coils attached to the scalp (Ahlfors & Ilmoniemi, 1989). The locations of the coils in relation to cardinal points on the head were determined with a 3-D digitizer (Polhemus Navigation Sciences, Colchester, VT).

During the experiment, the subjects were lying in a bed with their head inside a helmet-shaped instrument and were instructed to avoid any unnecessary movements, to ignore the sound stimuli, and to focus on watching a silent DVD (without subtitles) projected to the ceiling. The subjects were presented with harmonically rich tones that were delivered binaurally through plastic tubes and earplugs at the intensity of approximately 80 dB sound pressure level with a fixed 300-msec SOA (BrainStim software). The stimulus sequence consisted of standard tones ($p = .8$; 500-, 1000-, and 1500-Hz frequency components; 75-msec duration, including 5-msec rise and fall times) and deviant tones, which had either higher frequency ($p = .1$; 575, 1150- and 1725-Hz frequency components) or shorter duration ($p = .1$; 25-msec duration). The tones were presented in random order, except that each deviant tone was preceded by at least two standard tones. To control for exogenous effects on the MMN, we also included two control blocks (referred to hereafter as *control standards*; Kujala et al., 2007). In those, only the higher frequency and the shorter duration tones, which served as deviants in the oddball blocks, were presented at 100% probability.

On-line averaging of the MEG epochs (sampling rate 602 Hz, band-pass filtering 0.1–95 Hz) for the standard and deviant stimuli started 150 msec before and ended 350 msec after stimulus presentation. Epochs with MEG or EOG (recorded with electrodes placed above and below the left eye and lateral to the eyes) deflections exceeding 3000 fT/cm or 150 μV, respectively, were discarded from averaging. Recording was continued until approximately 100 accepted artifact-free trials for each deviant type were collected, which took about 10–15 min.

MEG Data Analysis

Data processing was performed blind to the group allocation of the patient. For data visualization, the averaged responses to the standard and deviant tones were first digitally filtered (band-pass 1–20 Hz) and baseline-corrected (time interval −50 to 0 msec before stimulus onset) and then, to adjust for head position variability between the measurement sessions, spatially corrected using the MaxFilter™ software (Elekta Neuromag, Helsinki, Finland). MMNm responses to changes in frequency and

duration (referred to hereafter as frequency MMNm and duration MMNm, respectively) were determined by subtracting the averaged responses to the control standard tones from the averaged responses to the deviant tones. By this arrangement, the subtraction procedure involves two acoustically identical sounds, which have been presented in different contexts (as standards and as deviants). Therefore, any difference in the brain activity they elicit can be attributed to memory-based processing and not to exogenous processes (see Kujala et al., 2007).

Source modeling of the MMNm responses was performed from the subtraction curves by using the minimum current estimation (MCE) method (Elekta Neuromag, Finland), which is based on minimum L1-norm estimates (Uutela, Hämäläinen, & Somersalo, 1999). MCE can be used without explicit information about the source location and can represent several local or distributed sources. In contrast, equivalent current dipole (ECD) models are guided by an a priori assumption that the signals measured in MEG are generated by a small number of focal sources that are known. Although this assumption may hold true for basic auditory responses in the normal brain, it may not be the case in a patient sample like ours where the majority (73%) of patients had cerebral damage extending to the temporal lobe. When first analyzing the baseline data, we found that the traditional ECD analysis was not able to reliably model the relatively small responses. Although spatially less accurate than the ECD, we found that the MCE could provide an overall measure of the strength of the MMNm response in both damaged and healthy hemispheres at different stages of recovery. Thus, we calculated the MCEs separately for each individual subject at each measurement session (1 week, 3 months, and 6 months poststroke). Averaged responses were first preprocessed by filtering with a 20-Hz low-pass digital filter and applying a prestimulus baseline (50 msec before stimulus onset) and a detrend baseline (300–350 msec from the stimulus onset) to eliminate the effects of noise. A spherical head model was used in calculating MCE solutions, which were then projected onto an averaged brain surface. The origin of this model was determined individually for each subject on the basis of a 3-D set of T1-weighted anatomical MRIs by fitting a sphere to the curvature of the outer surface of the brain.

After calculating the MCE, we identified the source of the MMNm in each hemisphere by selecting an ROI that produced the strongest response that was within the time window of 100–300 msec from tone onset and followed the vertical ("downward") dipolar orientation typical of the MMNm (Alho, 1995). However, we found that using the same ROI for each patient did not work because of the variability in lesion locations and individual recovery patterns of the MMNm. Our solution to this dilemma was to choose the ROI individually for each patient at each measurement sessions so that it always produced the highest amplitude response within the hemisphere (for a case example, see Figure 1A). The selection of the ROI was done using the graphical interface of the Neuromag MCE software, which allows you to select the range of patches by hand that you want to include in the ROI. This procedure was carefully performed in the same way each time, and the analyses were done by a single person (author T.S.) who was blinded to the group allocation of the patients. Naturally, the selection of the ROI was always guided by the knowledge where the MMN response is typically generated in the normal brain (Molholm, Martinez, Ritter, Javitt, & Foxe, 2005; Opitz, Rinne, Mecklinger, von Cramon, & Schröger, 2002; Rinne, Alho, Ilmoniemi, Virtanen, & Näätänen, 2000; Levänen, Ahonen, Hari, McEvoy, & Sams, 1996; Alho, 1995; Giard, Perrin, Pernier, & Bouchet, 1990). Thus, the ROIs that we used were primarily located in the temporal lobe, extending in some cases also frontally or parietally. MMNm latency was determined from the peak of the response. MMNm amplitude was determined as the mean amplitude within a 50-msec time window centered at the peak of the response.

Neuropsychological Testing

An extensive neuropsychological testing battery was used to evaluate cognitive recovery of the patients during the 6-month follow-up period (for details, see Särkämö et al., 2008). For the purpose of the present analyses, we included data from the verbal memory and focused attention domains because they were the only cognitive domains where significant improvement induced by the intervention was observed (Särkämö et al., 2008). Verbal memory was assessed using the story recall and word list learning tasks, and focused attention was assessed using the mental subtraction and Stroop subtests from the CogniSpeed© software.

Statistical Analyses

For the baseline (1 week poststroke) MMNm data, one-tailed *t* tests were conducted to determine whether the MMNm mean amplitudes differed significantly from zero. Group differences in baseline MMNm amplitudes and latencies were analyzed using two-way ANOVAs with Group (music, audio book, and control) and Lesion Laterality (left and right) as factors. Because the MMNm source was modeled separately for each hemisphere, separate ANOVAs were performed for left and right hemisphere MMNm responses. Changes in the MMNm amplitudes and latencies during recovery were analyzed using mixed-model ANOVAs with Time (1 week, 3 months, and 6 months) as a within-subjects factor and Group and Lesion Laterality as the between-subjects factors. The Greenhouse–Geisser epsilon was used to correct for sphericity. Significant differences across measurement sessions for the three groups were analyzed using tests of simple main effects with Bonferroni correction for multiple comparisons. In addition, post hoc tests (least significant difference [LSD]) were performed on change scores from the baseline to the 3-month stage and from the baseline to the 6-month stage. Also, the relationship between MMNm recovery

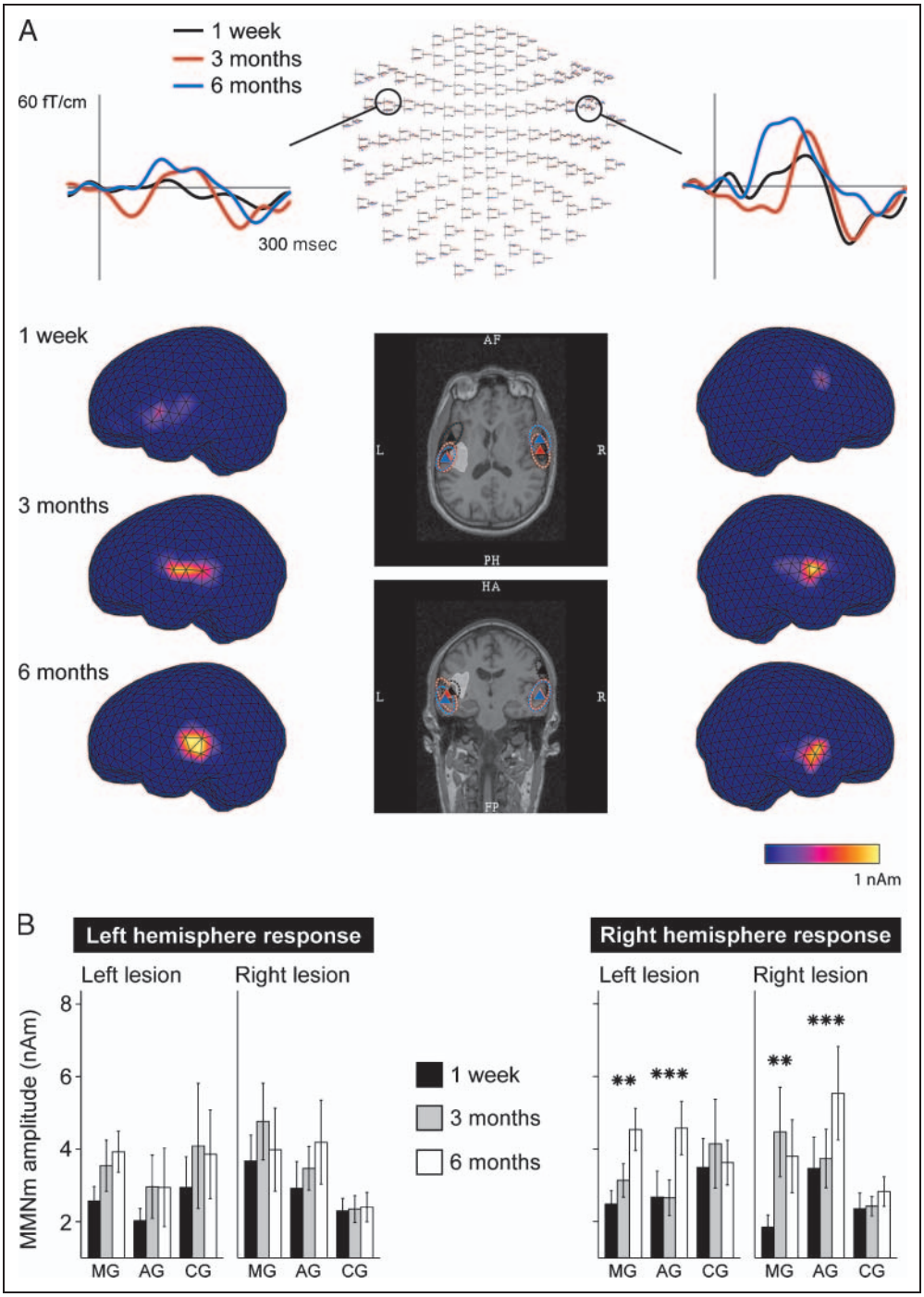

Figure 1. Frequency MMNm at different stages of stroke recovery. (A) A case example illustrating the typical recovery of the frequency MMNm. Changes in the strength of the MMNm in the left and right hemispheres are shown with subtraction curves from individual MEG channels over the temporal lobes and with source modeling performed using the MCE method. MRI images show the location of the lesion (white area) as well as the center (triangles) and the extent (ellipsoids) of the ROI used in the MCE analysis at the 1-week (black), 3-month (red), and 6-month (blue) poststroke stage. (B) Group results of the amplitude of the frequency MMNm source in the left and right hemispheres. Data (mean ± *SEM*) are shown separately for LHD and RHD patients. *$p < .05$, **$p < .01$, ***$p < .005$ Time main effect in a mixed-model ANOVA. MG = Music group; AG = Audio book group; CG = Control group.

and cognitive recovery was studied using Pearson and Spearman (for nonparametric variables) correlation coefficients (one-tailed). All statistical analyses were performed using SPSS (version 15.0). The level of statistical significance was set at $p < .05$.

RESULTS

MMNm Responses at the 1-Week Poststroke Stage

At the 1-week poststroke (baseline) stage, both frequency and duration deviants elicited MMNm responses that peaked around 150 msec. Across all patients, the MMNn mean amplitudes (Table 1) differed significantly from zero in both ipsilesional and contralesional hemispheres, $t(10) = 10.3–11.5$, $p < .0001$, but were generally smaller in the lesioned hemisphere. Two-way ANOVAs with Group (music, audio book, and control) and Lesion Laterality (left and right) as factors showed no significant main effects of Group, $F(2, 49) = 0.03–1.08$, $p = .31–.97$, or Lesion Laterality, $F(1, 49) = 0.02–3.62$, $p = .06–.88$, or significant Group × Lesion Laterality interactions, $F(2, 49) = 0.11–2.55$, $p = .09–.9$, for the frequency MMNm or duration

MMNm amplitudes or latencies. This confirms that the music, the audio book, and the control groups were comparable in MMNm parameters before the intervention.

Change in the Frequency MMNm during Recovery

For the amplitude of the frequency MMNm (Figure 1), a mixed-model ANOVA with Time (1 week, 3 months, and 6 months), Group, and Lesion Laterality as factors showed significant main effects of Time in both the left, $F(2, 96) = 4.26, p = .017$, and the right hemisphere, $F(2, 96) = 9.22$, $p = .0002$, and a significant Time × Group interaction in the right hemisphere, $F(4, 96) = 2.72, p = .034$. No significant main or interaction effects were observed for the latency of the frequency MMNm. Separate within-group analyses for the right hemisphere frequency MMNm amplitude showed that the main effect of time was significant in the music, $F(2, 34) = 5.81, p = .007$, and audio book, $F(1.4, 25.2) = 8.74, p = .003$, groups but not in the control group, $F(2, 32) = 0.25, p = .78$. Post hoc (Bonferroni) tests indicated that the MMNm amplitude increased significantly from the 1-week to the 6-month stage in both music ($p = .008$) and audio book ($p = .027$) groups. Also post hoc tests (LSD) of the change scores verified that the right hemisphere frequency MMNm amplitude increased significantly more in the music group ($p = .047$) and in the audio book group ($p = .049$) than in the control group during the 6-month recovery period but the music and the audio book did not differ from each other ($p = .96$). Thus, both music and audio book listening enhanced auditory sensory memory in the frequency domain during recovery.

Change in the Duration MMNm during Recovery

For the duration MMNm amplitude (Figure 2), there were no significant main effects of Time or Time × Group interactions. However, a significant Time × Group × Lesion Laterality interaction was observed in the right hemisphere, $F(4, 96) = 5.79, p = .0003$. No significant effects were observed for the latency of the duration MMN. Separate mixed-model ANOVAs for the left-hemisphere-damaged (LHD) and the right-hemisphere-damaged (RHD) patients revealed a significant Time × Group interaction for the right hemisphere duration MMNm amplitude only in RHD patients, $F(4, 52) = 4.16, p = .005$. Within the RHD patients, the Time main effect was significant in the audio book group, $F(2, 20) = 6.71, p = .006$, but not in the music, $F(2, 16) = 2.60, p = .11$, and control, $F(2, 16) = 1.18, p = .33$, groups. Post hoc (Bonferroni) tests indicated that the MMNm amplitude increment in the audio book group was significant from the 1-week to the 6-month stage ($p = .033$). Also, post hoc (LSD) tests of the change scores confirmed that within the RHD patients, the right hemisphere duration MMNm amplitude increased significantly more in the audio book group than in the control group ($p = .006$) and also marginally more in the audio book group than in the music group ($p = .054$) during the 6-month recovery period. Thus, audio book listening during recovery selectively enhanced auditory sensory memory in the duration domain but only in RHD patients.

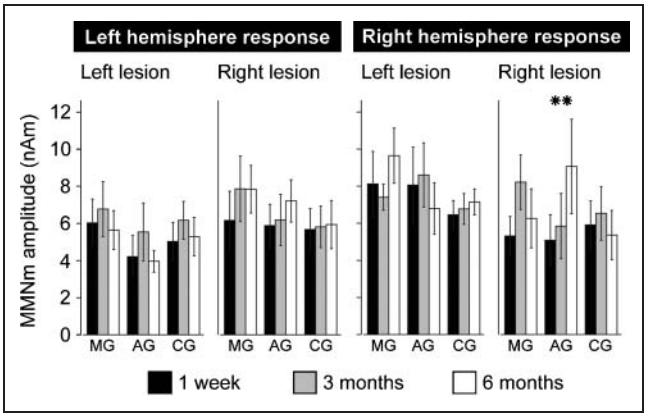

Figure 2. Group results of the duration MMNm amplitude at different stages of stroke recovery. Data (mean ± *SEM*) are shown separately for LHD and RHD patients. *$p < .05$, **$p < .01$, ***$p < .005$ Time main effect in a mixed-model ANOVA.

Correspondence between Cognitive and Sensory Recovery

To determine if the enhancement of the MMNm was related to the improved cognitive recovery induced by the intervention, we performed correlation analyses of the change scores of the MMNm amplitudes and neuropsychological tests from the 1-week to the 6-month stage. Because our previous findings (Särkämö et al., 2008) showed that the recovery of verbal memory and focused attention was better in the music group than in the audio book or control groups, we included only tests measuring these two domains in the correlation analyses. Similarly, only changes in the right hemisphere frequency MMNm amplitude were included because they were found to be greater in the music group than that in the control group. Although we also observed increased duration MMNm amplitudes in the audio book group, we did not correlate them to cognitive measures because the audio book and the control groups did not differ in their cognitive recovery (Särkämö et al., 2008).

Across all patients ($n = 54$), the increment of the right hemisphere frequency MMNm correlated significantly with improved performance on the delayed story recall (Pearson $r = .35, p = .005$) and mental subtraction (Spearman $r = .51, p = .0002$) tasks. To test if these relationships were due to the intervention, we performed the same correlation analyses separately for the music ($n = 18$), audio book ($n = 19$), and control groups ($n = 17$). As illustrated in Figure 3, the increased MMNm responses correlated with the recovery of immediate story recall in

the audio book group (Pearson $r = .41, p = .043$) and with the recovery of delayed story recall and mental subtraction both in the music group (Pearson $r = .46, p = .027$ and Spearman $r = .61, p = .011$, respectively) and in the audio book group (Pearson $r = .50$, $p = .015$ and Spearman $r = .49, p = .021$, respectively). In contrast, no significant positive correlations were observed between these tests and the MMNm in the control group ($r = -.11$ to $.37$, $p = .12$–$.41$). In fact, there was one significant negative correlation between changes in MMNm and word list learning in the control group (Pearson $r = -.60, p = .006$). Thus, these results suggest that the enhancement of the frequency MMNm response is related to the recovery of memory and attention and that this relationship is mediated by music and audio book listening.

DISCUSSION

According to the present findings, daily music or audio book listening after an MCA stroke can improve auditory sensory memory, as indexed by changes in the MMNm response measured with MEG during the 6-month poststroke period. Specifically, both patients who listened to music and patients who listened to audio books showed greater enhancement of the frequency MMNm amplitude in the right hemisphere as compared with patients who received no listening material. Because the music, the audio book, and the control groups were comparable before the intervention with respect to clinical and demographical variables (Särkämö et al., 2008) and MMNm parameters and they all also received equal amounts of other rehabilitation during the follow-up period (Särkämö et al., 2008), the enhancement of the MMNm can be reliably attributed to frequent exposure to music and audio books.

But what does the enhancement of the MMN response mean? Evidence from recent studies of healthy normal subjects and various clinical patient groups suggests that there is a robust relationship between early sensory processing and cognitive and psychosocial functioning (Light, Swerdlow, & Braff, 2007; Light & Braff, 2005). The MMN has been shown to correlate with behavioral performance on tasks of working memory, verbal learning, and executive performance in schizophrenia (Toyomaki et al., 2008; Kiang et al., 2007; Kawabuko et al., 2006; Baldeweg, Klugman, Gruzelier, & Hirsch, 2004), alcoholism (Ahveninen et al.,

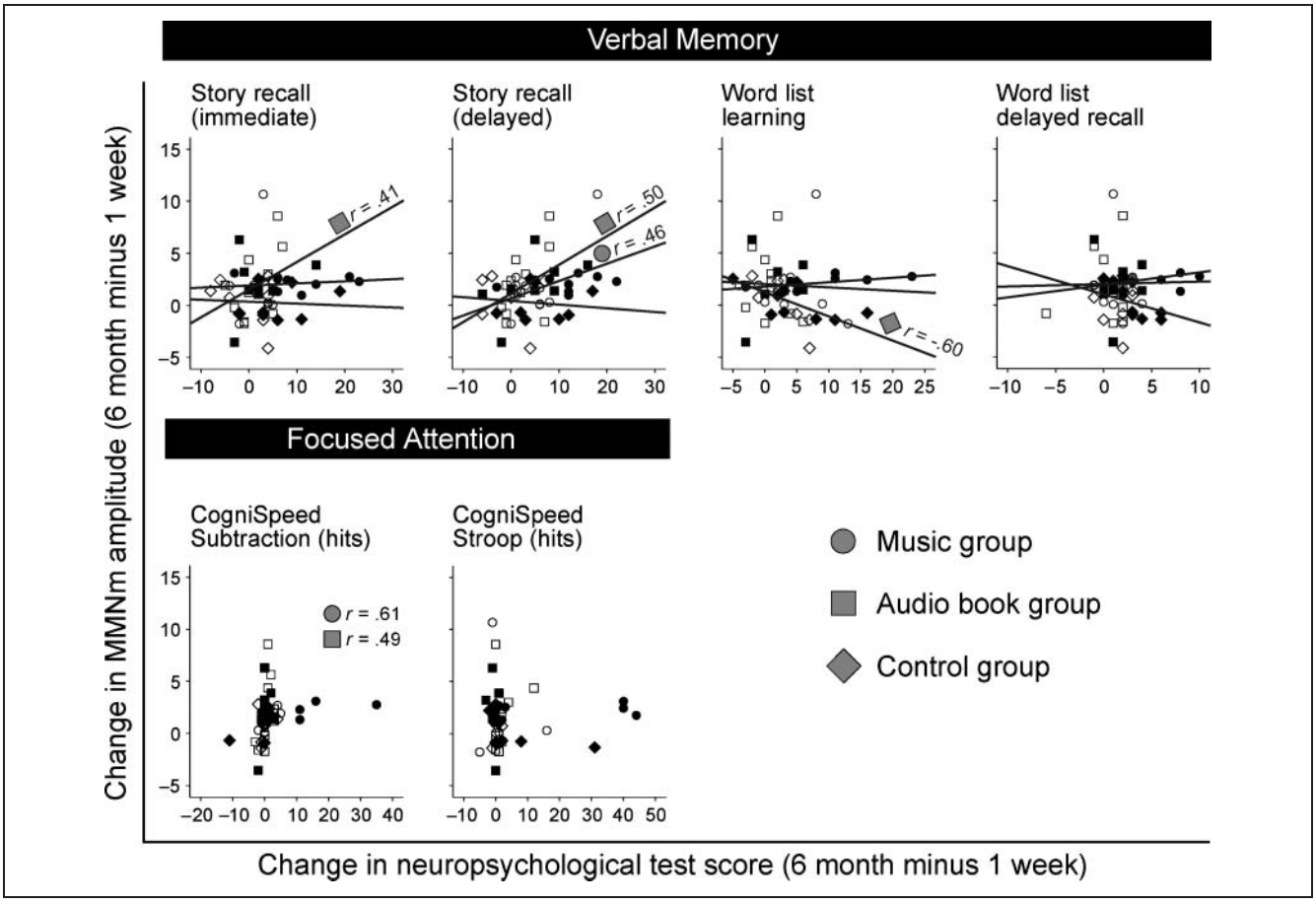

Figure 3. Correlations between the recovery of the right-hemisphere frequency MMNm, verbal memory, and focused attention during the 6-month poststroke period. Scatterplots of the change scores (6-month poststroke score minus 1-week poststroke score) are shown for the music group ($n = 18$, circles), the audio book group ($n = 19$, squares), and the control group ($n = 17$, diamonds) and for the LHD (filled) and RHD (unfilled) patients. Interpolation lines are shown only for Pearson correlation coefficients.

1999), and multiple sclerosis (Santos et al., 2006) and on speech production and comprehension in children (Mikkola et al., 2007; Jansson-Verkasalo et al., 2004; Kujala et al., 2001) and in aphasic patients (Pettigrew et al., 2005). Using a longitudinal design, Ilvonen et al. (2003) also have shown that changes in MMN correlate with the recovery of speech comprehension in aphasic stroke patients. As a potential mechanism underlying the relationship between MMN and cognition, Light et al. (2007) have proposed that efficiency at early sensory processing, indexed by the MMN, could free up cognitive resources for the successful encoding, retrieval, and discrimination of task-relevant information, which, in turn, could facilitate adaptive cognitive and social functioning.

Given this close coupling of the MMNm and cognition, we sought to determine if the enhancement of the frequency MMNm was related to the improved recovery of verbal memory and focused attention that we had observed in the music group previously (Särkämö et al., 2008). We found that the increment of the right hemisphere frequency MMNm correlated with behavioral improvement in the story recall and mental subtraction tasks. The reason why the MMN correlated with these tasks but not other tasks of verbal memory and focused attention (word list learning and delayed recall, Stroop) might be that story recall and mental subtraction place heavier demands on speech comprehension and working memory, which are both closely related to auditory sensory memory (Jääskeläinen et al., 2007). Notably, these positive correlations were observed both in the music group and in the audio book groups but not in the control group, suggesting that the link observed between changes in the MMNm, memory, and attention was mediated by an enriched auditory environment. Thus, it is possible that enhanced auditory sensory memory may be one potential mechanism that could account for the positive effect of music on cognitive recovery. However, because both music and audio book listening increased the MMNm and correlated with cognitive recovery whereas only music listening actually improved cognitive recovery (Särkämö et al., 2008), it is plausible that also other more music-specific mechanisms, such as improved arousal and mood, may underlie the better cognitive recovery induced by music. But what could be the neural basis for the effect of music and speech on auditory sensory memory?

One potential explanation is that frequent exposure to complex auditory stimuli, such as music and speech, could enhance the molecular and structural plasticity that normally takes place in the recovering brain. Animal studies have demonstrated that an enriched recovery environment can improve motor and cognitive recovery and induce many plastic changes, such as decreased infarct volume and increased neurogenesis (Nithianantharajah & Hannan, 2006; Johansson, 2004), especially if it contains also multimodal sensory stimuli (Maegele, Lippert-Gruener, Ester-Bode, Garbe, et al., 2005; Maegele, Lippert-Gruener, Ester-Bode, Sauerland, et al., 2005). Evidence from developmental animal studies also suggests that an enriched acoustic environment, in which the animal is frequently exposed to complex sounds, can improve both auditory cortical functions (Percaccio et al., 2005; Engineer et al., 2004) and nonauditory learning and memory (Angelucci, Fiore, et al., 2007; Chikahisa et al., 2006; Kim et al., 2006). Crucially, it can also increase neurogenesis and neurotrophin production in the brain (Angelucci, Fiore, et al., 2007; Angelucci, Ricci, et al., 2007; Chikahisa et al., 2006; Kim et al., 2006), both of which are important plasticity mechanisms also for stroke recovery in humans (Schäbitz et al., 2007; Jin et al., 2006). Furthermore, because listening to music (Flores-Gutiérrez et al., 2007; Brown, Martinez, & Parsons, 2004; Janata, Tillmann, & Bharucha, 2002; Blood, Zatorre, Bermudez, & Evans, 1999) and narrated stories (Lindenberg & Scheef, 2007; Schmithorst, Holland, & Plante, 2006; Tzourio-Mazoyer, Josse, Crivello, & Mazoyer, 2004; Papathanassiou et al., 2000; Mazoyer et al., 1993) activates a widespread network of temporal, prefrontal, premotor, and parietal cortical areas that are mainly supplied by the MCA, regular listening after an MCA stroke could also promote recovery by stimulating the peri-infarct and contralesional regions. These regions typically show increased plasticity and susceptibility to environmental influence in the early recovery stage (Kreisel, Bäzner, & Hennerici, 2006).

Another potential mechanism that could account for the facilitating effect of music and speech on auditory sensory memory is enhanced glutamatergic neurotransmission. Glutamate is the primary excitatory amino transmitter in the cortex that plays a critical role in learning and the initiation of long-term memory formation through its action at *N*-methyl-D-aspartate (NMDA) receptors (Cotman, Monaghan, & Ganong, 1988). Drug studies have demonstrated that NMDA antagonists have a strong influence on MMN generation in mice (Ehrlichman, Maxwell, Majumdar, & Siegel, 2008), rats (Tikhonravov et al., 2008), monkeys (Javitt, Steinschneider, Schroeder, & Arezzo, 1996), and healthy human subjects (Korostenskaja, Nikulin, Kičić, Nikulina, & Kähkönen, 2007; Umbricht, Koller, Vollenweider, & Schmid, 2002; Kreitschmann-Andremahr et al., 2001). Similarly, conditions like Alzheimer's disease, stroke, and schizophrenia that are known to decrease the MMN (Turetsky et al., 2007; Ilvonen et al., 2003; Pekkonen, 2000) are also accompanied by dysfunctions in the NMDA receptor system. Interestingly, animal studies have recently shown that an enriched sound environment can enhance glutamate expression and receptor function in the AC and the anterior cingulate (Nichols et al., 2007; Xu et al., 2007), whereas auditory deprivation can decrease NMDA receptor expression levels in the AC (Bi et al., 2006). Because changes in glutamate transmission also parallel the recovery from brain infarction (Centonze et al., 2007; Keyvani & Schallert, 2002), glutamate may thus be a crucial neural factor linking auditory stimulation, changes in MMNm and memory, and stroke recovery observed in the present study.

In addition to these structural plasticity mechanisms, also top–down mechanisms could play a role in mediating the effect of music and audio book listening on auditory sensory memory. Neuroimaging studies have shown that the sources of the MMN to tones are mostly located bilaterally in the superior temporal gyrus and in the right frontal and parietal areas (Molholm et al., 2005; Opitz et al., 2002; Rinne et al., 2000; Levänen et al., 1996). The sources in the temporal areas might be involved in largely automatic processing of the changes on the acoustic properties of the sound, whereas the sources on the frontal and parietal areas might reflect the switching of attention and thus be more sensitive to attentional effects (Restuccia, Della Marca, Marra, Rubino, & Valeriani, 2005). Consistent with this, enhanced attention due to auditory training (Atienza, Cantero, & Dominguez-Marin, 2002) or nonauditory mental training, such as concentrative meditation (Srinivasan & Baijal, 2007), can increase the amplitude of the MMN. In principle, it is thus possible that in the present study the MMN could have been facilitated by concurrent recovery of cognitive functions, especially attention. However, only music listening was found to improve cognitive recovery (Särkämö et al., 2008), whereas the MMN was enhanced by both music and audio book listening. Moreover, the beneficial effect of music on cognitive recovery could be partly mediated by the affective dopaminergic system, which, however, does not seem to play a significant role in MMN generation (Garrido, Kilner, Stephan, & Friston, 2009). In addition, we recorded the MMNm in an entirely passive task using MEG, which does not detect frontal sources very well (Rinne et al., 2000). These facts suggest that the observed correlation between increased MMNm amplitude and cognitive recovery could be driven more by bottom–up than top–down factors.

In addition to the effect of music and audio books on the frequency MMNm, the audio book listeners also showed larger gains in the duration MMNm in the damaged right hemisphere than the other patient groups. However, because there were no differences between the audio book and the control groups in their cognitive recovery (Särkämö et al., 2008), it seems that the effect of audio book listening is limited to low-level temporal auditory processing and may be language specific. Previous EEG and MEG studies have shown that speakers of "quantity languages" (e.g., Finnish, Japanese), where the duration of phonemes is crucial for semantic speech perception, have larger MMN responses to small duration differences both in nonspeech (Tervaniemi et al., 2006) and in speech sounds (Menning, Imaizumi, Zwitserlood, & Pantev, 2002) than speakers of nonquantity languages (e.g., German). Moreover, active training with temporally modified speech can enhance speech discrimination ability in healthy language learners (Menning et al., 2002) as well as in language-learning impaired children (e.g., Tallal & Gaab, 2006). Thus, it is possible that regular exposure to the temporal acoustic cues that are embedded in speech could lead to language-dependent plasticity also after stroke.

Interestingly, significant effects of listening on both frequency MMNm and duration MMNm were observed only in the right hemisphere. Because listening to music (Flores-Gutiérrez et al., 2007; Brown et al., 2004; Janata et al., 2002; Blood et al., 1999) and narrated stories (Lindenberg & Scheef, 2007; Schmithorst et al., 2006; Tzourio-Mazoyer et al., 2004; Papathanassiou et al., 2000; Mazoyer et al., 1993) activates the brain mostly bilaterally, this is not likely due to differences in the stimulation of the left and right hemispheres. Instead, it may be related to the general observation that the MMN (or MMNm) response to tones is typically stronger on the right hemisphere than on the left hemisphere (Levänen et al., 1996; Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991; Giard et al., 1990). There is also some evidence from functional neuroimaging (PET and fMRI) studies indicating that both duration and frequency discrimination may activate the right hemisphere more than the left (Nenadic et al., 2003; Griffiths, Johnsrude, Dean, & Green, 1999), especially when the stimuli are relatively easy to discriminate (Reiterer et al., 2005) like the ones we used in the present study (see Tervaniemi et al., 1999, 2005). Coupled with the fact that the lesions of our patients were, on the average, slightly larger in the right than that in the left hemisphere, this could explain why significant listening-induced plasticity effects on the MMNm were seen only in the right hemisphere. Furthermore, we found that audio book listening enhanced the right hemisphere duration MMNm in RHD patients but not in LHD patients. This may be due to the fact that the majority (69%) of LHD patients in the present study had at least minor aphasia. Because aphasic patients typically have difficulties in the comprehension of complex speech and also show diminished MMNm responses especially to duration changes (Pettigrew et al., 2005; Ilvonen et al., 2003), it is possible that they did not benefit from the stimulation provided by the audio books like the RHD patients, at least with regards to low-level temporal auditory processing.

In conclusion, the results of the present study demonstrate, to our knowledge for the first time, that frequent listening to music and audio books after neural damage can enhance auditory sensory memory, as indexed by changes in MMNm amplitude. Moreover, this enhanced recovery of early sensory processing may be one crucial neural mechanism underlying the positive effect of music on cognitive recovery (Särkämö et al., 2008). Clinically, the results encourage the use of music in neurological rehabilitation.

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REFERENCES

Ahlfors, S., & Ilmoniemi, R. J. (1989). Magnetometer position indicator for multichannel MEG (pp. 693–696). In *Proceedings of the 7th International Conference on Biomagnetism,* held 13–18 August in New York.

Ahveninen, J., Jääskeläinen, I. P., Pekkonen, E., Hallberg, A., Hietanen, M., Mäkelä, R., et al. (1999). Suppression of mismatch negativity by backward masking predicts impaired working-memory performance in alcoholics. *Alcoholism, Clinical and Experimental Research, 23,* 1507–1514.

Alho, K. (1995). Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. *Ear and Hearing, 16,* 38–51.

Alho, K., Sams, M., Paavilainen, P., Reinikainen, K., & Näätänen, R. (1989). Event-related brain potentials reflecting processing of relevant and irrelevant stimuli during selective listening. *Psychophysiology, 26,* 514–528.

Amenedo, E., & Escera, C. (2000). The accuracy of sound duration representation in the human brain determines the accuracy of behavioural perception. *European Journal of Neuroscience, 12,* 2570–2574.

Angelucci, F., Fiore, M., Ricci, E., Padua, L., Sabino, A., & Tonali, P. A. (2007). Investigating the neurobiology of music: Brain-derived neurotrophic factor modulation in the hippocampus of young adult mice. *Behavioural Pharmacology, 18,* 491–496.

Angelucci, F., Ricci, E., Padua, L., Sabino, A., & Tonali, P. A. (2007). Music exposure differentially alters the levels of brain-derived neurotrophic factor and nerve growth factor in the mouse hypothalamus. *Neuroscience Letters, 429,* 152–155.

Atienza, M., Cantero, J. L., & Dominguez-Marin, E. (2002). The time course of neural changes underlying auditory perceptual learning. *Learning & Memory, 9,* 138–150.

Baldeweg, T., Klugman, A., Gruzelier, J., & Hirsch, S. R. (2004). Mismatch negativity potentials and cognitive impairment in schizophrenia. *Schizophrenia Research, 69,* 203–217.

Bi, C., Cui, Y., Mao, Y., Dong, S., Zhang, J., & Sun, X. (2006). The effect of early auditory deprivation on the age-dependent expression pattern of NR2B mRNA in rat auditory cortex. *Brain Research, 1110,* 30–38.

Blood, A. J., Zatorre, R. J., Bermudez, P., & Evans, A. C. (1999). Emotional responses to pleasant and unpleasant music correlate with activity in paralimbic brain regions. *Nature Neuroscience, 2,* 382–387.

Brown, S., Martinez, M. J., & Parsons, L. M. (2004). Passive music listening spontaneously engages limbic and paralimbic systems. *NeuroReport, 15,* 2033–2037.

Centonze, D., Rossi, S., Tortiglione, A., Picconi, B., Prosperetti, C., De Chiara, V., et al. (2007). Synaptic plasticity during recovery from permanent occlusion of the middle cerebral artery. *Neurobiology of Disease, 27,* 44–53.

Chikahisa, S., Sei, H., Morishima, M., Sano, A., Kitaoka, K., Nakaya, Y., et al. (2006). Exposure to music in the perinatal period enhances learning performance and alters BDNF/TrkB signaling in mice as adults. *Behavioural Brain Research, 169,* 312–319.

Cotman, C. W., Monaghan, D. T., & Ganong, A. H. (1988). Excitatory amino acid neurotransmission: NMDA receptors and Hebb-type synaptic plasticity. *Annual Review of Neuroscience, 11,* 61–80.

Cowan, N. (1988). Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system. *Psychological Bulletin, 104,* 163–191.

Csépe, V., Osman-Sági, J., Molnár, M., & Gósy, M. (2001). Impaired speech perception in aphasic patients: Event-related potential and neuropsychological assessment. *Neuropsychologia, 39,* 1194–1208.

Deouell, L. Y., Bentin, S., & Soroker, N. (2000). Electrophysiological evidence for an early (pre-attentive) information processing deficit in patients with right hemisphere damage and unilateral neglect. *Brain, 123,* 353–365.

Ehrlichman, R. S., Maxwell, C. R., Majumdar, S., & Siegel, S. J. (2008). Deviance-elicited changes in event-related potentials are attenuated by ketamine in mice. *Journal of Cognitive Neuroscience, 20,* 1403–1414.

Engineer, N. D., Percaccio, C. R., Pandya, P. K., Moucha, R., Rathbun, D. L., & Kilgard, M. P. (2004). Environmental enrichment improves response strength, threshold, selectivity, and latency of auditory cortex neurons. *Journal of Neurophysiology, 92,* 73–82.

Flores-Gutiérrez, E. O., Díaz, J. M., Barrios, F. A., Favila-Humara, R., Guevara, M. A., del Río-Portilla, Y., et al. (2007). Metabolic and electric brain patterns during pleasant and unpleasant emotions induced by music masterpieces. *International Journal of Psychophysiology, 65,* 69–84.

Garrido, M. I., Kilner, J. M., Stephan, K. E., & Friston, K. J. (2009). The mismatch negativity: A review of underlying mechanisms. *Clinical Neurophysiology, 120,* 453–463.

Giard, M. H., Perrin, F., Pernier, J., & Bouchet, P. (1990). Brain generators implicated in the processing of auditory stimulus deviance: A topographic event-related potential study. *Psychophysiology, 27,* 627–640.

Griffiths, T. D., Johnsrude, I., Dean, J. L., & Green, G. G. R. (1999). A common neural substrate for the analysis of pitch and duration pattern in segmented sound? *NeuroReport, 10,* 3825–3830.

Ilvonen, T. M., Kujala, T., Kiesiläinen, A., Salonen, O., Kozou, H., Pekkonen, E., et al. (2003). Auditory discrimination after left-hemisphere stroke: A mismatch negativity follow-up study. *Stroke, 34,* 1746–1751.

Jääskeläinen, I. P., Ahveninen, J., Belliveau, J. W., Raij, T., & Sams, M. (2007). Short-term plasticity in auditory cognition. *Trends in Neurosciences, 30,* 653–661.

Janata, P., Tillmann, B., & Bharucha, J. J. (2002). Listening to polyphonic music recruits domain-general attention and working memory circuits. *Cognitive, Affective, and Behavioral Neuroscience, 2,* 121–140.

Jansson-Verkasalo, E., Korpilahti, P., Jäntti, V., Valkama, M., Vainionpää, L., Alku, P., et al. (2004). Neurophysiologic correlates of deficient phonological representations and object naming in prematurely born children. *Clinical Neurophysiology, 115,* 179–187.

Jaramillo, M., Paavilainen, P., & Näätänen, R. (2000). Mismatch negativity and behavioural discrimination in humans as a function of the magnitude of change in sound duration. *Neuroscience Letters, 290,* 101–104.

Javitt, D. C., Steinschneider, M., Schroeder, C. E., & Arezzo, J. C. (1996). Role of cortical *N*-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: Implications for schizophrenia. *Proceedings of the National Academy of Sciences, U.S.A., 93,* 11962–11967.

Jin, K., Wang, X., Xie, L., Mao, X. O., Zhu, W., Wang, Y., et al. (2006). Evidence for stroke-induced neurogenesis in the human brain. *Proceedings of the National Academy of Sciences, U.S.A., 103,* 13198–13202.

Johansson, B. B. (2004). Functional and cellular effects of environmental enrichment after experimental brain infarcts. *Restorative Neurology and Neuroscience, 22,* 163–174.

Kawabuko, Y., Kasai, K., Kudo, N., Rogers, M. A., Nakagome, K., Itoh, K., et al. (2006). Phonetic mismatch negativity predicts verbal memory deficits in schizophrenia. *NeuroReport, 17,* 1043–1046.

Keyvani, K., & Schallert, T. (2002). Plasticity-associated molecular and structural events in the injured brain. *Journal of Neuropathology and Experimental Neurology, 61,* 831–840.

Kiang, M., Light, G. A., Prugh, J., Coulson, S., Braff, D. L., & Kutas, M. (2007). Cognitive, neurophysiological, and functional correlates of proverb interpretation abnormalities in schizophrenia. *Journal of the International Neuropsychological Society, 13,* 653–663.

Kim, H., Lee, M. H., Chang, H. K., Lee, T. H., Lee, H. H., Shin, M. C., et al. (2006). Influence of prenatal noise and music on the spatial memory and neurogenesis in the hippocampus of developing rats. *Brain & Development, 28,* 109–114.

Korostenskaja, M., Nikulin, V. V., Kičić, D., Nikulina, A. V., & Kähkönen, S. (2007). Effects of NMDA receptor antagonist memantine on mismatch negativity. *Brain Research Bulletin, 72,* 275–283.

Kreisel, S. H., Bäzner, H., & Hennerici, M. G. (2006). Pathophysiology of stroke rehabilitation: Temporal aspects of neuro-functional recovery. *Cerebrovascular Diseases, 21,* 6–17.

Kreitschmann-Andermahr, I., Rosburg, T., Demme, U., Gaser, E., Nowak, H., & Sauer, H. (2001). Effect of ketamine on the neuromagnetic mismatch field in healthy humans. *Cognitive Brain Research, 12,* 109–116.

Kujala, T., Karma, K., Ceponiene, R., Belitz, S., Turkkila, P., Tervaniemi, M., et al. (2001). Plastic neural changes and reading improvement caused by audio-visual training in reading-impaired children. *Proceedings of the National Academy of Sciences, U.S.A., 98,* 10509–10514.

Kujala, T., Tervaniemi, M., & Schröger, E. (2007). The mismatch negativity in cognitive and clinical neuroscience: Theoretical and methodological considerations. *Biological Psychology, 74,* 1–19.

Levänen, S., Ahonen, A., Hari, R., McEvoy, L., & Sams, M. (1996). Deviant auditory stimuli activate human left and right auditory cortex differently. *Cerebral Cortex, 6,* 288–296.

Light, G. A., & Braff, D. L. (2005). Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. *Archives of General Psychiatry, 62,* 127–136.

Light, G. A., Swerdlow, N. R., & Braff, D. L. (2007). Preattentive sensory processing as indexed by the MMN and P3a brain responses is associated with cognitive and psychosocial functioning in healthy adults. *Journal of Cognitive Neuroscience, 19,* 1624–1632.

Lindenberg, R., & Scheef, L. (2007). Supramodal language comprehension: Role of the left temporal lobe for listening and reading. *Neuropsychologia, 45,* 2407–2415.

Maegele, M., Lippert-Gruener, M., Ester-Bode, T., Garbe, J., Bouillon, B., Neugebauer, E., et al. (2005). Multimodal early onset stimulation combined with enriched environment is associated with reduced CNS lesion volume and enhanced reversal of neuromotor dysfunction after traumatic brain injury in rats. *European Journal of Neuroscience, 21,* 2406–2418.

Maegele, M., Lippert-Gruener, M., Ester-Bode, T., Sauerland, S., Schäfer, U., Molcany, M., et al. (2005). Reversal of neuromotor and cognitive dysfunction in an enriched environment combined with multimodal early onset stimulation after traumatic brain injury in rats. *Journal of Neurotrauma, 22,* 772–782.

Mazoyer, B. M., Tzourio, N., Frak, V., Syrota, A., Murayama, N., Levrier, O., et al. (1993). The cortical representation of speech. *Journal of Cognitive Neuroscience, 5,* 467–479.

Menning, H., Imaizumi, S., Zwitserlood, P., & Pantev, C. (2002). Plasticity of the human auditory cortex induced by discrimination learning of non-native, mora-timed contrasts of the Japanese language. *Learning & Memory, 9,* 253–267.

Mikkola, K., Kushnerenko, E., Partanen, E., Serenius-Sirve, S., Leipälä, J., Huotilainen, M., et al. (2007). Auditory event-related potentials and cognitive function of preterm children at five years of age. *Clinical Neurophysiology, 118,* 1494–1502.

Molholm, S., Martinez, A., Ritter, W., Javitt, D. C., & Foxe, J. J. (2005). The neural circuitry of pre-attentive auditory change-detection: An fMRI study of pitch and duration mismatch negativity generators. *Cerebral Cortex, 15,* 545–551.

Näätänen, R. (1991). Mismatch negativity (MMN) outside strong attentional focus: A commentary on Woldorff et al. *Psychophysiology, 28,* 478–484.

Näätänen, R., Paavilainen, P., Rinne, T., & Alho, K. (2007). The mismatch negativity (MMN) in basic research of central auditory processing: A review. *Clinical Neurophysiology, 118,* 2544–2590.

Nenadic, I., Gaser, C., Volz, H. P., Rammsayer, T., Hager, F., & Sauer, H. (2003). Processing of temporal information and the basal ganglia: New evidence from fMRI. *Experimental Brain Research, 148,* 238–246.

Nichols, J. A., Jakkamsetti, V. P., Salgado, H., Dinh, L., Kilgard, M. P., & Atzori, M. (2007). Environmental enrichment selectively increases glutamatergic responses in layer II/III of the auditory cortex of the rat. *Neuroscience, 145,* 832–840.

Nithianantharajah, J., & Hannan, A. J. (2006). Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nature Reviews Neuroscience, 7,* 697–709.

Novitski, N., Tervaniemi, M., Huotilainen, M., & Näätänen, R. (2004). Frequency discrimination at different frequency levels as indexed by electrophysiological and behavioral measures. *Cognitive Brain Research, 20,* 26–36.

Opitz, B., Rinne, T., Mecklinger, A., von Cramon, D. Y., & Schröger, E. (2002). Differential contribution of frontal and temporal cortices to auditory change detection: fMRI and ERP results. *Neuroimage, 15,* 167–174.

Paavilainen, P., Alho, K., Reinikainen, K., Sams, M., & Näätänen, R. (1991). Right hemisphere dominance of different mismatch negativities. *Electroencephalography & Clinical Neurophysiology, 78,* 466–479.

Papathanassiou, D., Etard, O., Mellet, E., Zago, L., Mazoyer, B., & Tzourio-Mazoyer, N. (2000). A common language network for comprehension and production: A contribution to the definition of language epicenters with PET. *Neuroimage, 11,* 347–357.

Pekkonen, E. (2000). Mismatch negativity in aging and in Alzheimer's and Parkinson's diseases. *Audiology & Neuro-otology, 5,* 216–224.

Percaccio, C. R., Engineer, N. D., Pruette, A. L., Pandya, P. K., Moucha, R., Rathbun, D. L., et al. (2005). Environmental enrichment increases paired-pulse depression in rat auditory cortex. *Journal of Neurophysiology, 94,* 3590–3600.

Pettigrew, C. M., Murdoch, B. E., Kei, J., Ponton, C. W., Alku, P., & Chenery, H. J. (2005). The mismatch negativity (MMN) response to complex tones and spoken words in individuals with aphasia. *Aphasiology, 19,* 131–163.

Reiterer, S. M., Erb, M., Droll, C. D., Anders, S., Ethofer, T., Grodd, W., et al. (2005). Impact of task difficulty on lateralization of pitch and duration discrimination. *NeuroReport, 16,* 239–242.

Restuccia, D., Della Marca, G., Marra, C., Rubino, M., & Valeriani, M. (2005). Attentional load of the primary task influences the frontal but not the temporal generators of mismatch negativity. *Cognitive Brain Research, 25,* 891–899.

Rinne, T., Alho, K., Ilmoniemi, R. J., Virtanen, J., & Näätänen, R. (2000). Separate time behaviors of the temporal and frontal mismatch negativity sources. *Neuroimage, 12,* 14–19.

Santos, M. A., Munhoz, M. S., Peixoto, M. A., Haase, V. G., Rodrigues, J. L., & Resende, L. M. (2006). Mismatch negativity contribution in multiple sclerosis patients. *Revista Brasileira de Otorrinolaringologia, 72,* 800–807.

Särkämö, T., Tervaniemi, M., Laitinen, S., Forsblom, A., Soinila, S., Mikkonen, M., et al. (2008). Music listening enhances cognitive recovery and mood after middle cerebral artery stroke. *Brain, 131,* 866–876.

Schäbitz, W. R., Steigleder, T., Cooper-Kuhn, C. M., Schwab, S., Sommer, C., Schneider, A., et al. (2007). Intravenous brain-derived neurotrophic factor enhances poststroke sensorimotor recovery and stimulates neurogenesis. *Stroke, 38,* 2165–2172.

Schmithorst, V. J., Holland, S. K., & Plante, E. (2006). Cognitive modules utilized for narrative comprehension in children: A functional magnetic resonance imaging study. *Neuroimage, 29,* 254–266.

Srinivasan, N., & Baijal, S. (2007). Concentrative meditation enhances preattentive processing: A mismatch negativity study. *NeuroReport, 18,* 1709–1712.

Tallal, P., & Gaab, N. (2006). Dynamic auditory processing, musical experience and language development. *Trends in Neurosciences, 29,* 382–390.

Tervaniemi, M., Jacobsen, T., Röttger, S., Kujala, T., Widmann, A., Vainio, M., et al. (2006). Selective tuning of cortical sound-feature processing by language experience. *European Journal of Neuroscience, 23,* 2538–2541.

Tervaniemi, M., Lehtokoski, A., Sinkkonen, J., Virtanen, J., Ilmoniemi, R. J., & Näätänen, R. (1999). Test–retest reliability of mismatch negativity for duration, frequency and intensity changes. *Clinical Neurophysiology, 110,* 1388–1393.

Tervaniemi, M., Sinkkonen, J., Virtanen, J., Kallio, J., Ilmoniemi, R. J., Salonen, O., et al. (2005). Test–retest stability of the magnetic mismatch response (MMNm). *Clinical Neurophysiology, 116,* 1897–1905.

Tiitinen, H., May, P., Reinikainen, K., & Näätänen, R. (1994). Attentive novelty detection in humans is governed by pre-attentive sensory memory. *Nature, 370,* 90–92.

Tikhonravov, D., Neuvonen, T., Pertovaara, A., Savioja, K., Ruusuvirta, T., Näätänen, R., et al. (2008). Effects of an NMDA-receptor antagonist MK-801 on an MMN-like response recorded in anesthetized rats. *Brain Research, 1203,* 97–102.

Toyomaki, A., Kusumi, I., Matsuyama, T., Kako, Y., Ito, K., & Koyama, T. (2008). Tone duration mismatch negativity deficits predict impairment of executive function in schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 32,* 95–99.

Turetsky, B. I., Calkins, M. E., Light, G. A., Olincy, A., Radant, A. D., & Swerdlow, N. R. (2007). Neurophysiological endophenotypes of schizophrenia: The viability of selected candidate measures. *Schizophrenia Bulletin, 33,* 69–94.

Tzourio-Mazoyer, N., Josse, G., Crivello, F., & Mazoyer, B. (2004). Interindividual variability in the hemispheric organization for speech. *Neuroimage, 21,* 422–435.

Umbricht, D., Koller, R., Vollenweider, F. X., & Schmid, L. (2002). Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. *Biological Psychiatry, 51,* 400–406.

Uutela, K., Hämäläinen, M., & Somersalo, E. (1999). Visualization of magnetoencephalographic data using minimum current estimates. *Neuroimage, 10,* 173–180.

van Praag, H., Kempermann, G., & Gage, F. H. (2000). Neural consequences of environmental enrichment. *Nature Reviews Neuroscience, 1,* 191–198.

Xu, F., Cai, R., Xu, J., Zhang, J., & Sun, X. (2007). Early music exposure modifies GluR2 protein expression in rat auditory cortex and anterior cingulate cortex. *Neuroscience Letters, 420,* 171–183.