Neurophysiological predictors of aphasia recovery in patients with large left-hemispheric infarction: a mismatch negativity study

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Abstract

Background: Although the rehabilitation of aphasia has been extensively studied, the prediction of language outcome still has not received sufficient attention. The aim of this study was to predict the language outcome using mismatch negativity (MMN) in patients with large left-hemispheric infarction.

Methods: MMN was elicited by an oddball paradigm in which a standard tone (1000 Hz) and deviant tone (1500 Hz) were presented at 90% and 10% of the number of tones, respectively. The mean amplitudes and laterality indexes (LIs) of MMN were measured over the prefrontal, frontal, central, parietal, temporal, and perisylvian areas during the first 7 days (session 1) and 10 to 20 days (session 2) post-onset. Mixed three-way analysis of variance (ANOVA) was used to investigate differences in these factors between two aphasia groups (the good recovery group and poor recovery group). The predictive value of the most significant LI was also compared with the score of National Institutes of Health Stroke Scale score and low-density volume on computed tomography.

Results: A total of 18 patients were enrolled in this study. Mixed three-way ANOVA showed no interaction effect of session × region of interest (ROI) × group (F [3.59, 57.38] = 1.301, P = 0.282) and no interaction effect of ROI × group (F [1.81, 29.01] = 0.71, P = 0.487) and session × group (F [1.00, 16.00] = 0.084, P = 0.776) for MMN amplitude. No interaction effect of session × ROI × group (F [1.79, 28.58] = 0.62, P = 0.530), but an interaction effect of session × group (F [1.00, 16.00] = 5.21, P = 0.036) was found for LIs. In the poor recovery group, the LIs of MMN over all the ROIs, except the parietal area, became more negative at session 2 than those at session 1 (P < 0.05), but this effect was not observed in the good recovery group. Additionally, significant differences were observed in the LIs at session 2 between the two groups (P < 0.05). The LI over the perisylvian area at session 2 had the highest predictive value with an area under the curve of 0.963 (95% confidence interval: 0.884–1.000). An LI score > −0.36 over the perisylvian area suggested good recovery, but a score < −0.36 suggested poor recovery. The LI cut-off value of −0.36 had the highest sensitivity (90.0%) and specificity (87.5%) for predicting a good language outcome at 3 months post-stroke.

Conclusion: LIs of MMN amplitudes at approximately 2 weeks post left-hemisphere stroke serve as more sensitive predictors of language outcome, among which the LI over the perisylvian area exhibits the best predictive value.

Keywords: Mismatch negativity; Stroke; Laterality index; Aphasia

Introduction

Large hemispheric infarction (LHI), including sub-total or complete infarction in the territory of the middle cerebral artery (MCA) territory with or without involvement of the anterior or posterior cerebral artery territories, is found in up to 10% of patients with supratentorial ischemia.[1] Global aphasia, which adversely affects the efficacy of rehabilitation therapy and quality of life, is often a concomitant disorder along with severe hemiplegia in patients with left LHI. Although aphasia recovery has received considerable attention,[2,3] no good predictors of language outcomes currently exist.

Although clinical factors, including age, lesion characteristics, education, and possibly sex, have been established for predicting aphasia recovery,[4,5] they are insensitive or contradictory. Taken together, these factors explain approximately 40% of the variance.[4] Moreover, anatomical predictors have been studied for aphasia recovery,[2,6] but for critical patients with LHI, undergoing a functional magnetic resonance imaging (MRI) examination is difficult or not feasible. Therefore, other predictors should be explored for these severely aphasic patients.

As a non-invasive functional imaging technique with high temporal resolution, electroencephalography (EEG) is a good choice for studying auditory discrimination as it...
MCA determined by computed tomography (CT) or MRI; with a volume of at least 2/3 of the territory of the left hemisphere; consecutively included in this study. Subjects were enrolled Eighteen patients with left LHI were prospectively and retrospectively enrolled. All the subjects provided informed consent. Xuanwu Hospital (No. [2016] 03). The closest relatives of the patients with left LHI. In this perspective case-control study, we aimed to use MMN amplitude and laterality indexes (LLs) to predict the aphasia outcome in patients with left LHI.

Methods

Ethical approval

This study was approved by the Ethical Committee of Xuanwu Hospital (No. [2016] 03). The closest relatives of all the subjects provided informed consent.

Participants

Eighteen patients with left LHI were prospectively and consecutively included in this study. Subjects were enrolled according to the following inclusion criteria: (i) left LHI with a volume of at least 2/3 of the territory of the left MCA determined by computed tomography (CT) or MRI; (ii) first onset; (iii) right-handedness judged by the Edinburgh Handedness Inventory; (iv) 18 to 80 years old; (v) native Mandarin Chinese speaker living in Beijing or the surrounding areas; (vi) an aphasia severity rating of 0 according to the aphasia severity rating scale (ASRS) of the Boston diagnostic aphasia examination (BDAE) when the patient recovered to wakefulness within the first 20 days; and (vii) no obvious cognitive dysfunction before the stroke. The exclusion criteria were: (i) patients who received decompressive craniectomy; (ii) patients with history of neuropsychiatric disorders; (iii) left LHI accompanied by right hemispheric infarction or posterior circulation infarction; (iv) no N100 in the bilateral hemispheres; (v) administration of sedatives within 24 h before EEG data collection; (vi) severe complications such as electrolyte and metabolic disturbances, seizures or others; or (vii) loss to follow-up.

Clinical information, including age, sex, intra-vascular therapy, low-density volume on CT, National Institutes of Health (NIH) Stroke Scale (NIHSS) score and whether the patient underwent decompressive craniectomy, was collected. All the patients were followed up for 3 months, and the ASRS of the BDAE was used to determine the severity of aphasia at the second collection session and 3 months post-stroke. The ASRS consists of a six-point Likert scale with 0 as the lowest score (no usable speech or auditory comprehension) and 5 as the best score (minimal discernible speech handicap). All patients were divided into two groups according to the score at 3 months, the good recovery group (ASRS score ≥1) and the poor recovery group (ASRS score = 0).

Stimulus paradigm

Since auditory discrimination was the basis of auditory comprehension and complex language processes, we chose the typical oddball paradigm with pure tones to induce MMN, which were generated by E-Prime 3.0 software (PST Inc., Sharpsburg, PA, USA) and presented binaurally via insert earphones. The stimuli consisted of standard and frequency-deviant pure tones both at an intensity of 70 dB sound pressure level (SPL). The standard stimulus, which represented 90% of the total stimuli, had a frequency of 1000 Hz, and the deviant stimulus, representing 10% of the total stimuli, had a frequency of 1500 Hz. The duration of both stimuli was 50 ms, and the inter-stimulus interval was 600 ms.

EEG data collection and analysis

EEG data were collected over two sessions: the first session took place during the first 7 days and the second session occurred at 10 to 20 days post-onset. EEG data were continuously recorded with a 64-electrode EEG wireless 64A system and NicoletOne software (Nicolet, Madison, WI, USA) according to the extended international 10–20 system. Electrode impedance was maintained below 5 Ω. Continuous EEG data were online-filtered with a bandpass of 0.05 to 70 Hz, sampled at 512 Hz and online referenced to CPz.

EEG data were analyzed as event-related potentials (ERPs) using the EEGLAB toolbox loaded in MATLAB R2015b (Mathworks Inc., Natick, Massachusetts, USA). ERP pre-processing, averaging and analysis were all undertaken in EEGLAB 14.1. Offline pre-processing included bandpass filtering (0.05–30.00 Hz) and referencing to the averaged left and right mastoids (M1 and M2). Independent components analysis was performed using the “runica” algorithm from EEGLAB, and eye movements and blinking artifacts were subtracted. The continuous EEG data were epoched from 100 ms pre-stimulation to 500 ms post-stimulation (−100 to 500 ms), and baseline correction was performed using the baseline pre-stimulation. Epochs containing artifacts greater than ±100 μV were rejected. The individual sweeps of every participant were averaged for standard and deviant stimuli separately, and the difference waveforms were obtained by subtracting the standard-ERP from the deviant-ERP. Grand average waveforms were also calculated for both aphasic groups.

unfolds over a timescale of milliseconds and does not require a behavioral response.[7] Furthermore, this electrophysiological method allows access to direct measures of neuronal activity, and the spectrotemporal information of the brain’s activity can provide insights into neural function and neuroplasticity.[9] Mismatch negativity (MMN) is an automatic brain response to deviant or infrequent changes in the acoustic environment, with a latency of 100 to 250 ms after stimulus onset.[10] Evidence has revealed that MMN has good replicability even at the individual level[10], therefore, it may be reliable for clinical use. Various studies have revealed that the MMN response has been used as a probe for speech processing,[11] other cognitive functions,[12] and even in the prediction of disorders of consciousness.[13] MMN has also been confirmed as a useful tool for mapping functional language recovery after left-hemisphere stroke, mostly during the chronic recovery stage.[14] The potential of MMN as a biomarker for predicting neurofunctional outcomes and monitoring neurorehabilitation is largely unexplored. MMN may provide some valuable information regarding the integrity of auditory processes in the early stage of stroke when the patient is not yet able to fully cooperate.[15] Therefore, we hypothesized that MMN can serve as a neurophysiological predictor of aphasia in patients with left LHI. In this perspective case-control study, we aimed to use MMN amplitude and laterality indexes (LLs) to predict the aphasia outcome in patients with left LHI.
MMN peaks were visually identified as the most negative deflection between 100 and 200 ms post-stimulation. The peak latency was defined as the time that MMN peaks appeared. The MMN peak latency for each subject was measured at the Fz electrode, and peak amplitudes were measured over the midline area (Fz, Cz, Pz), left-hemisphere (AF3, AF7, F3, F5, C3, S3, P3, P5, FT7, TP7) and right hemisphere (AF4, AF8, F4, F6, C4, S4, P4, P6, FT8, TP8). The mean amplitudes were calculated for each region of interest (ROI), including the anterior frontal (AF3/4, AF7/8), frontal (F3/4, F5/6), central (C3/4, C5/6), parietal (P3/4, P5/6), temporal (FT7/8, TP7/8), perisylvian (F5/6, C5/6, P5/6, FT7/8, TP7/8), and each hemisphere (all selected electrodes on each side). To further explore the laterality effects, LIs were calculated using the formula \((L - R)/(L + R)\) for each ROI.

**Statistical analysis**

The MMN amplitudes and LIs of the two groups at each session were compared using mixed three-way analysis of variance (ANOVA), with session (two levels: session 1, session 2) and ROI (15 levels for the amplitude analysis and seven levels for the LI analysis) as within-subject factors and Group (two levels: poor recovery and good recovery) as the between-subject factor. P values and degrees of freedom were determined based on Geisser-Greenhouse correction when the sphericity hypothesis was not met. Receiver operating characteristic (ROC) curves were also used to identify the most predictive factor. Statistical analysis was performed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA), and significance was defined as \(P < 0.05\).

**Mismatch negativity**

For each session, no significant differences were found between the numbers of standard or deviant trials of both groups (all \(P > 0.05\)). The difference waveforms are shown in Figure 1.

MMN amplitudes were normally distributed for each session and group. The mixed three-way ANOVA showed no interaction effect of session \(\times\) ROI \(\times\) group (\(F = 3.59, P = 0.01\); \(P = 0.282\)) and no interaction effect of ROI \(\times\) group (\(F = 1.81, 29.01 = 0.71, P = 0.487\)) and session \(\times\) group (\(F = 1.00, 16.00 = 0.084, P = 0.776\), suggesting that the absolute amplitude of MMN was not a good predictor of language outcome.

**Results**

**Clinical characteristics**

The sites of lesions in all the patients included the frontal, temporal, insular, and parietal cortices, basal ganglia, and sub-cortical structures (internal capsule, deep white matter) to various degrees. The ASRS score at 3-month post-stroke was 0 in eight patients, 1 in seven patients, and 2 in three patients. No significant differences were found in sex (male: female ratio = 5:3 vs. 6:4) and age (72.88 ± 4.39 years vs. 70.60 ± 4.83 years, \(t = 1.032, P = 0.317\)) between the two aphasia groups. There was no significant difference in the collection time between the two groups (4.13 ± 2.41 days vs. 3.50 ± 1.35 days, \(t = 0.696, P = 0.497\) for session 1; 14.75 ± 1.39 days vs. 14.20 ± 2.62 days, \(t = 0.654, P = 0.527\) for session 2). All patients received no recanalization therapy or failed to get recanalization [Table 1].

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**Table 1: Demographic characteristics and clinical findings of the patients.**

| Patient No., sex, age (years) | Interval of onset-therapy (h) | Recanalization therapy | Type of aphasia | Lesion site | Volume of low density on CT (cm³) | NIHSS at session 1 | NIHSS at session 2 | DC surgery | Baseline ASRS | 3 months-ASRS |
|-------------------------------|-------------------------------|------------------------|----------------|------------|----------------------------------|-------------------|------------------|------------|--------------|--------------|
| 1, M, 69                      | 13.0                          | NO                     | GA             | FTOPOIB    | 565.8                            | 26                | 22               | N          | 0            | 0            |
| 2, F, 72                      | 10.0                          | NO                     | GA             | FTPIB      | 556.3                            | 23                | 21               | N          | 0            | 0            |
| 3, M, 78                      | 1.5                           | IVT + MT, failed       | GA             | FTPOI      | 553.1                            | 26                | 22               | N          | 0            | 0            |
| 4, M, 69                      | 10.0                          | NO                     | GA             | FTOB       | 462.9                            | 26                | 21               | N          | 0            | 0            |
| 5, M, 79                      | 2.5                           | IVT, failed            | GA             | FTPIB      | 549.2                            | 23                | 21               | N          | 0            | 0            |
| 6, M, 69                      | 9.0                           | NO                     | GA             | FPTIB      | 550.5                            | 23                | 21               | N          | 0            | 0            |
| 7, F, 77                      | 10.0                          | NO                     | GA             | FTIB       | 593.3                            | 26                | 22               | Y          | 0            | 0            |
| 8, F, 70                      | 3.0                           | IVT, failed            | GA             | FTPIB      | 487.9                            | 23                | 21               | N          | 0            | 0            |
| 9, F, 74                      | 10.0                          | NO                     | GA             | FTPIB      | 460.4                            | 24                | 22               | N          | 0            | 0            |
| 10, M, 68                     | 10.0                          | NO                     | GA             | FPTIB      | 438.4                            | 23                | 21               | N          | 1            | 1            |
| 11, F, 76                     | 4.0                           | IVT, failed            | GA             | TPOB       | 492.0                            | 23                | 21               | N          | 0            | 1            |
| 12, M, 76                     | 8.0                           | NO                     | BA             | FTIB       | 455.2                            | 23                | 21               | N          | 0            | 1            |
| 13, F, 70                     | 4.5                           | IVT, failed            | GA             | FPTOB      | 498.2                            | 23                | 21               | N          | 0            | 1            |
| 14, F, 75                     | 11.0                          | NO                     | GA             | FTPIB      | 447.0                            | 23                | 21               | N          | 0            | 1            |
| 15, M, 70                     | 3.0                           | IVT + MT, failed       | GA             | FTPIB      | 551.0                            | 26                | 22               | Y          | 0            | 1            |
| 16, M, 64                     | 14.0                          | NO                     | BA             | FTIB       | 446.5                            | 23                | 21               | N          | 0            | 2            |
| 17, M, 64                     | 3.5                           | IVT + MT, failed       | GA             | FTPIB      | 476.0                            | 23                | 21               | N          | 0            | 2            |
| 18, M, 66                     | 9.0                           | NO                     | GA             | FTIB       | 488.5                            | 23                | 21               | N          | 0            | 2            |

NIHSS: National Institutes of Health Stroke Scale; DC: Decompressive craniectomy; ASRS: Aphasia severity rating scale; M: Male; F: Female; NO: No recanalization therapy; IVT: Intra-venous thrombolysis; MT: Mechanical thrombectomy; GA: Global aphasia; BA: Broca’s aphasia; F: Frontal; T: Temporal; P: Parietal; O: Occipital; I: Insular; B: Basal ganglion; Y: Yes; N: No.
LIs of MMN were also normally distributed for each session and group. For the LIs of MMN, no interaction effect of session × ROI × group (F[1.79, 28.58] = 0.62, P = 0.530) was found, but an interaction effect of session × group (F[1.00, 16.00] = 5.21, P = 0.036) was observed. In the poor recovery group, the LIs at all ROIs except the parietal area, were significantly different between session 1 and session 2, and the LIs of session 2 were significantly decreased compared to those of session 1 (inter-hemispheric: \(d = -0.401 \pm 0.138, \ P = 0.010\); prefrontal: \(d = -0.354 \pm 0.138, \ P = 0.021\); frontal: \(d = -0.381 \pm 0.127, \ P = 0.008\); central: \(d = -0.365 \pm 0.130, \ P = 0.013\); temporal: ...
Laterality indexes; MMN: Mismatch negativity. 

The ROC curve analysis showed that the LI of the perisylvian electrodes had the greatest predictive value, with the highest area under the curve (AUC) of 0.963 (95% confidence interval: 0.884–1.000). ROC curve analysis including the perisylvian LI, low-density volume, and NIHSS scores were also performed, and among these variables, the perisylvian LI had the highest predictive value for the 3-month language outcome. The AUCs of low-density volume and NIHSS score at session 1 and session 2 for predicting good language recovery were 0.138 (P = 0.010), 0.325 (P = 0.214), and 0.350 (P = 0.286), respectively. The cut-off value of the perisylvian LI with the highest sensitivity and specificity was –0.36. An LI score >–0.36 at the perisylvian ROI suggested good language recovery, and a score <–0.36 suggested poor language outcome (Figure 2).

Discussion

Our study investigated electrophysiological predictors of the 3-month language outcome in patients with left LHI. Three findings were revealed: first, MMN at approximately 2 weeks, but not within 7 days, is more valuable for predicting the language outcome. Second, the LI is more sensitive as a good predictor than absolute amplitudes of MMN and clinical characteristics. Third, the LI of the perisylvian area at approximately 2 weeks has the greatest predictive value.

More reliable time point for language outcome prediction

Interestingly, according to our results, in some patients, MMN was apparent over the left-hemisphere at session 1 but dampened or improved at session 2; however, in other patients, MMN was absent at session 1 but appeared or was still absent at session 2. This observation may be caused by brain edema in the first days post-stroke. During the first 7 days, patients with LHI consistently suffer from different extents of brain edema and overall metabolic depression, which dampen neural processes and affect...
brain electrical activity. In patients with effective compensation via enhanced branch circulation after vascular occlusion, brain edema is less severe, and neurofunction can be restored after the edema period. However, in patients with inadequate branch compensation, excessive perfusion or hemorrhagic transformation after recanalization, brain function cannot recover or even deteriorate. In other words, the electrical activity of neurons fluctuates during the brain edema period, resulting in poor prediction of the language outcome.

To some extent, our result is consistent with the previous findings indicating that measurement fluctuations occurred within 2 weeks from stroke onset due to clinical-physiological processes and the influence of psychodynamic mechanisms. This result is also similar to that of a study conducted by Ilvonen et al in which they described decreases or improvements in MMN amplitudes on the 10th day compared to those on the 4th-day post-stroke. Their study also revealed a significant correlation between changes in BDAE percentiles and MMN amplitudes from the 10th day to the 3-month measurements, suggesting that after brain edema, MMN amplitudes can reflect language function. Therefore, MMN amplitudes after brain edema subsides may be predictive of the language outcome.

Moreover, the observed MMN results in the first 7 days may also be correlated with increased glutaminergic activity after stroke, which caused the higher LIs of MMN elicited at the first session for the poor language recovery group. Pharmacological studies have demonstrated that MMN is under glutaminergic modulation. Glutaminergic excitotoxicity is a significant contributor to cell death during acute stroke and is associated with over-activation of N-Methyl-D-Aspartate glutamate receptors. Good recovery from aphasia is more strongly correlated with the function of the left-hemisphere. Indeed, converging evidence supports that during the recovery phase, successful restoration of language networks depends on efficient reintegration of ipsilateral language-related areas or their neighboring regions, but not recruitment of new regions. Right hemispheric activation may be caused by insufficient recovery attempts or reduced transcallosal inhibition from the left side. According to this theory, the outcome of language recovery outcome predominantly depends on residual function and compensatory activation in the left-hemisphere. Our result that a larger LI corresponds to a better language outcome also supports the predominant role of the left-hemisphere in language recovery. More severe impairment of language areas in the left-hemisphere corresponds to a greater requirement for compensation from their right homologs. Greater activation of the right hemisphere leads to a lower LI, indicating a poor language outcome.

**Brain regions related to language recovery**

Our findings that LIs of MMN over any selected ROIs at 2 weeks post-infarction were predictors of language outcome suggest not only a relationship between the impairment extent of these regions and language outcome but also the essential roles of these regions in language processing. A larger LI corresponds to better activity of the left brain or decreased compensation of the right hemisphere. A higher predictive value of the LI over an ROI suggests that the region plays a more essential role in language recovery.

Neural processes underlying language recovery are still obscure. Brain areas around lesions in the left-hemisphere, right middle temporal gyrus, inferior frontal gyrus (IFG), bilateral prefrontal cortex, and left cingulate gyrus have been all reported to participate in aphasia recovery.

**Brain hemisphere(s) associated with language recovery**

We did not find that the MMN amplitudes were predictive of the language outcome, which is consistent with previous studies. In contrast, the LIs of MMN amplitudes overall selected ROIs at 10 to 20 days were good predictors of the 3-month language recovery, indicating that the LIs of MMN were more sensitive than the amplitudes. The LI score depends on MMN amplitudes over the bilateral hemispheres. A higher LI indicates better function of the left side or weaker compensation of the right side, and vice versa, suggesting that language function may be related not only to the activity of the left-hemisphere but also the right homologous regions. However, MMN amplitude only reflects the function of a certain brain area, but not the extent of difference in bilateral hemisphere.

Evidence from structural and functional neuroimaging studies has revealed that both ipsilateral and contralateral anatomical structures and metabolic factors are related to aphasia recovery. Moreover, aphasia recovery after stroke is a dynamic process in which the right hemisphere is important for longitudinal outcomes. While multiple studies have reported activation of right hemispheric regions in patients with aphasia post-stroke, its contribution to language recovery seems subsidiary. Good recovery from aphasia is more strongly correlated with the function of the left-hemisphere. Indeed, converging evidence supports that during the recovery phase, successful restoration of language networks depends on efficient reintegration of ipsilateral language-related areas or their neighboring regions, but not recruitment of new regions. Right hemispheric activation may be caused by insufficient recovery attempts or reduced transcallosal inhibition from the left side. According to this theory, the outcome of language recovery outcome predominantly depends on residual function and compensatory activation in the left-hemisphere. Our result that a larger LI corresponds to a better language outcome also supports the predominant role of the left-hemisphere in language recovery. More severe impairment of language areas in the left-hemisphere corresponds to a greater requirement for compensation from their right homologs. Greater activation of the right hemisphere leads to a lower LI, indicating a poor language outcome.

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A previous study found that in a dichotic paradigm, a generator in the prefrontal cortex accounted for considerable variance of the scalp potential during the later MMN period (120–200 ms), which supports the role of the prefrontal cortex in MMN generation. The prefrontal MMN generator is activated when the deviance detection system in the temporal cortex experiences dysfunction in discriminating stimuli. Alain et al suggested that auditory discrimination was bilaterally impaired in patients with lesions in prefrontal regions. Furthermore, speech comprehension has been demonstrated to be a complex process and involves an interaction between relatively automatic perceptual processes and strategic top-down control, the core of which is the prefrontal cortex. Another study also suggests that prefrontal control of language processing is enhanced after aphasia. In addition, due to their cellular similarity to and anatomical continuity with the supratemporal gyrus, the supramarginal gyrus and angular gyrus play essential roles in the recovery of auditory comprehension and are the initial compensatory structures during the stage of aphasia recovery stage. Moreover, the right IFG was more reliably recruited when the left inferior frontal cortex was
lesioned. The perisylvian language area consist of several structures, including the IFG, superior temporal gyrus, angular gyrus, and supramarginal gyrus. These structures work together to contribute to the language recovery. Impairments of the perisylvian area in the left hemisphere, the core of the language network, can result in difficulties in nearly all domains of language processing. Thus, the perisylvian area plays the most crucial role in overall language recovery.

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Conflicts of interest
None.

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