N400 responses of children with primary language disorder: intervention effects

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Event-related brain potentials were examined in 6 to 8-year-old children with primary language disorder before and after a 5-week narrative-based language intervention. Participants listened to sentences ending with semantically congruous or incongruous words. By comparison with typical controls, the children with primary language disorder exhibited no pretreatment differences in their N400 responses to congruous and incongruous sentence-final words. After intervention, the typical incongruous–congruous difference was observable owing to a dramatic reduction in the amplitude of the N400 response to congruous words. These characteristic changes in brain responses may reflect a positive effect of the language intervention on the lexical–semantic processing skills in children with language impairment. *NeuroReport* 20:1104–1108 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Primary language disorder (PLD) is a developmental disorder manifested by oral receptive and/or expressive language deficits, low normal or better nonverbal cognitive skills (IQ > 70), and no other frank motor or sensory disorders [1]. The prevalence of PLD is not known, but English-speaking children with specific language impairment (SLI), a subset of PLD, constitute approximately 7% of the population, at kindergarten age [2].

Numerous reports have indicated that these children have deficits in early auditory cortical responses (e.g. the N1–P2 complex) related to poor temporal processing or frequency discrimination of verbal and nonverbal stimuli, but the pattern of deficit varies considerably across studies (see Ref. [3]). Fewer studies have examined later response components, such as N400, associated with processing of verbal stimuli among these children. The N400 is a centro-parietal negativity with latency between 0.3 and 0.5 s after stimulus onset that is larger in response to incongruous than congruous target words in sentences [4,5]. It is considered to be associated with lexical integration of information in target words with other key information presented earlier in the text. This response among children with PLD is a matter of some dispute. Using visually presented sentences, Neville *et al.* [6] observed that N400 responses for both incongruous and congruous terminal words, as well as their difference (termed as 'semantic effect') were larger in PLD than controls. In contrast, Sabisch *et al.* [7] used an auditory task and reported significant N400 activity but no semantic effect in children with PLD. This absence was because of a large N400 response to congruous sentences. This suggests that for the children with PLD, considerable effort was required to integrate target words with context even when the words were highly predictable. In a visual semantic task, Ors *et al.* [8] found a similar N400 noneffect among fathers of children with SLI, and interpreted it as a possible residual marker of past language deficiencies.

The first objective of the present investigation was to determine which of these patterns would be observed in a small sample of 6 to 8-year-old children with PLD who participated in a larger investigation of language intervention efficacy. The second objective was to ascertain whether an intervention designed to improve PLD children's ability to comprehend, retell, and generate multiepisode stories and to use complex grammar as required in stories has an impact on the neuronal processes underlying the N400 semantic effect. The intervention, termed as narrative-based language intervention (NBLI, [9]), exposed children to and challenged them to produce coherent stories in which information at each story stage must be integrated with information already presented. Thus, we hypothesized that the children's N400 responses would appear more typical after a period of intervention.

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Methods

All aspects of this project were carried out following the guidelines and with the approval of the University of Kansas Medical Center Human Subjects Committee. The experiments were conducted with the written assent of each participant and consent of each child's caregiver.

Participants

Only children with normal hearing and no history of neurological disorder were included. Participants with PLD ($n = 9$) took part in the second year of a 2-year summer-time project in which they received NBLI as either their sole treatment or their first of a two-part treatment. Five of the nine children were randomly assigned to a group that began NBLI 6 weeks after the other four participants started the intervention. This 6-week wait provided a no-treatment control condition. Participants received no other interventions over the course of the treatment period. One child was excluded from the analysis because he provided a very low number of correct responses in one condition of the event-related potentials (ERPs) study, reflecting the possibility that he did not follow the task instructions or did not pay attention to the stimuli. All data presented in this study refer to the remaining group of eight PLD participants.

These children had just completed kindergarten or first grade (mean age = 7 years, 9 months, SD = 5.7 months) and were receiving speech-language services or undergoing testing to determine the need for such services. Based on the Test of Language Development – primary: 3, they had mean spoken language quotients of 68.8 (SD = 5.6) and mean listening quotients of 82.4 (SD = 9.8).

Five children met the traditional criteria for SLI with standard scores on the nonverbal matrices subtest of the Kaufman Brief Intelligence Test Second Edition (KBIT2) of 85 or higher and three, who are best described as having nonspecific language impairment (NLI), had scores between 73 and 84. Children with NLI tend to have language profiles similar to those of children with SLI, but they are often more severe [10]. They respond to behavioral treatments in ways similar to children with SLI [11].

Typically developing (TD) children ($n = 9$) whose parents had indicated a willingness to participate in research and who lived in area codes served by the same schools attended by most of the children with PLD were ascertained for this study. Two of these control participants were excluded from the ERP analysis because of the presence of excessive artifacts. The remaining seven TD children (mean age = 7 years, 8 months, SD = 10.9 months) had average KBIT2 scores of 107.7 (SD = 9.1), Spoken Language Quotients test scores of 107.0 (SD = 10.4), and Language Quotient scores of 110.0 (SD = 9.8).

The structure of NBLI

The children with PLD took part in 10–12 sessions of NBLI over a 5-week period. Each session was centered around a specifically created story, which contained three pictures and a text with a high concentration of grammatical forms selected as treatment goals. Each lesson involved (i) listening to the story and retelling it, with clinician scaffolding of story content and target grammatical forms; (ii) imitation of sentences containing target forms found in the story of the day; and (iii) cogeneration of a novel story.

Experimental testing

Children's performances on a standard battery of behavioral and ERP tests were measured immediately before and after NBLI. The main behavioral measure to be analyzed for this report is the Narrative Language Ability Index (NLAI), which is a standardized composite of narrative comprehension (NC) and oral narration (ON) scores from the Test of Narrative Language [12]. Two measures for grammar were based on the language sample data: the mean main verb score from the Developmental Sentence Score [13], and the proportion of sentences containing a clausal connective other than 'and' and 'then'.

The ERP experiment consisted of two conditions, each containing 51 sentences. The sentences were created in pairs to be identical in every respect except for the last word, which was either congruous or incongruous with the meaning of the rest of the sentence [e.g. When it's cold, Dad will wear his (pause) coat/ball]. The target word in each sentence was preceded by a silent pause of 750 ms. A semantic cue related to the congruous target word was present in both the initial phrase/subordinate clause (e.g. When it's cold) and the independent clause (e.g. Dad will wear his …). Thus, each congruous target was highly predictable but not generally fully determinable. All incongruous targets represented distinctly different semantic classes. Sentences spoken by a female native English speaker were digitized into audio files and were presented in a mixed, random order through a loudspeaker, using the STIM 2 software (Compumedics Neuroscan, El Paso, Texas, USA).

The EEG was recorded using 16 Ag/AgCl electrodes positioned according to the 10–20 International System [14], at three midline sites, five sites over each hemisphere, left and right mastoid (the left mastoid served as physical reference), and forehead (ground). Vertical and horizontal electro-oculograms were separately recorded with bipolar montages. Electrode impedances were kept below 10 kΩ, and the sampling rate was 300 Hz.

To minimize the risk of data contamination by movement artifacts, participants took part in a delayed-response comprehension task. Before testing, children were introduced to a cartoon of a human girl, Liza, and an alien, Lulu, who has the ability to sound like Liza but sometimes says funny things. After a break of 1800 ms after each sentence offset, a visual stimulus prompted participants to press one of the two buttons to indicate whether the sentence was spoken by Liza (congruous) or Lulu (incongruous).

The total recording time was approximately 15 min. Short breaks (approximately 30 s to 1 min) were given every 20 trials (approximately 3 min) to minimize the risk of a decrease in participant cooperation owing to fatigue. Questions or concerns were answered during these breaks, and instructions were reinforced when necessary.

Data analysis

EEG data were re-referenced off-line to the linked-mastoids. The signals were divided into epochs from −500 to 1200 ms relative to the onset of the last word in each sentence. Epochs contaminated by blinks, eye movement artifacts, or other high-amplitude activity exceeding 100 μV were rejected. Digital filters (bidirectional 4th order Butterworth) were used to filter the data between 0.35 and 20 Hz. Epochs were averaged separately for the congruous and incongruous conditions. Amplitudes were evaluated relative to the corresponding 100-ms prestimulus baseline.

The semantic effect was defined as the difference between mean ERP amplitudes for the incongruous and congruous stimuli computed within the 300–600 ms time window. Primary statistical analyses were analyses of variance with the semantic effect as the dependent variable, and with α set at 0.10. To minimize the risk of type 1 error, tests were performed only at three midline sites (Fz, Cz, Pz). Correlation analyses were conducted to test the relationship between the semantic effect and behavioral scores. Each regression analysis was performed by testing for the presence of extreme standardized residuals to identify and eliminate potential outliers.

Results

Behavioral performance

For PLD participants, the average number of correct responses in the behavioral judgment component of the ERP task was: 40.8 (SD = 3.5; congruous) and 42.8 (SD = 2.9; incongruous) pre-NBLI, and 43.4 (SD = 2.6; congruous) and 40.5 (SD = 5.5; incongruous) post-NBLI. For control participants, the average number of correct responses was 42.6 (SD = 3.4; congruous) and 43.1 (SD = 6.3; incongruous). The TD group did not differ significantly from the PLD group either pre-NBLI [$F(1,13) < 1.0$; $P > 0.33$] or post-NBLI [$F(1,13) < 0.76$; $P > 0.40$]. In addition, no condition effect was observed for either the PLD [pre-NBLI: $F(1,7) = 2.7$; $P = 0.14$; post-NBLI: $F(1,7) = 2.48$; $P = 0.16$] or TD [$F(1,6) = 0.2$; $P = 0.69$] groups. However, a significant effect of Time was present for PLD participants in the congruous condition [$F(1,7) = 5.7$; $P = 0.05$], whereas such an effect was not present in the incongruous condition [$F(1,7) = 1.8$; $P = 0.22$].

The PLD participants significantly improved their NLAIs from 79.0 pre-NBLI to 86.88 post-NBLI [$t(7) = 2.9$; $P = 0.02$]. This reflected significant gains in both NC [$t(7) = 2.6$; $P = 0.04$] and ON [$t(7) = 2.9$; $P = 0.02$]. No significant gains were observed in grammatical measures [$t(7) < 0.8$; $P < 0.4$].

N400 responses

The average number of artifact-free trials across all sessions and conditions was 35.9 (SD = 6.5) for the PLD participants and 33.3 (SD = 8.6) for the TD participants. Between-group differences (when split also by condition) were not statistically significant [$F(1,13) < 0.63$; $P > 0.44$].

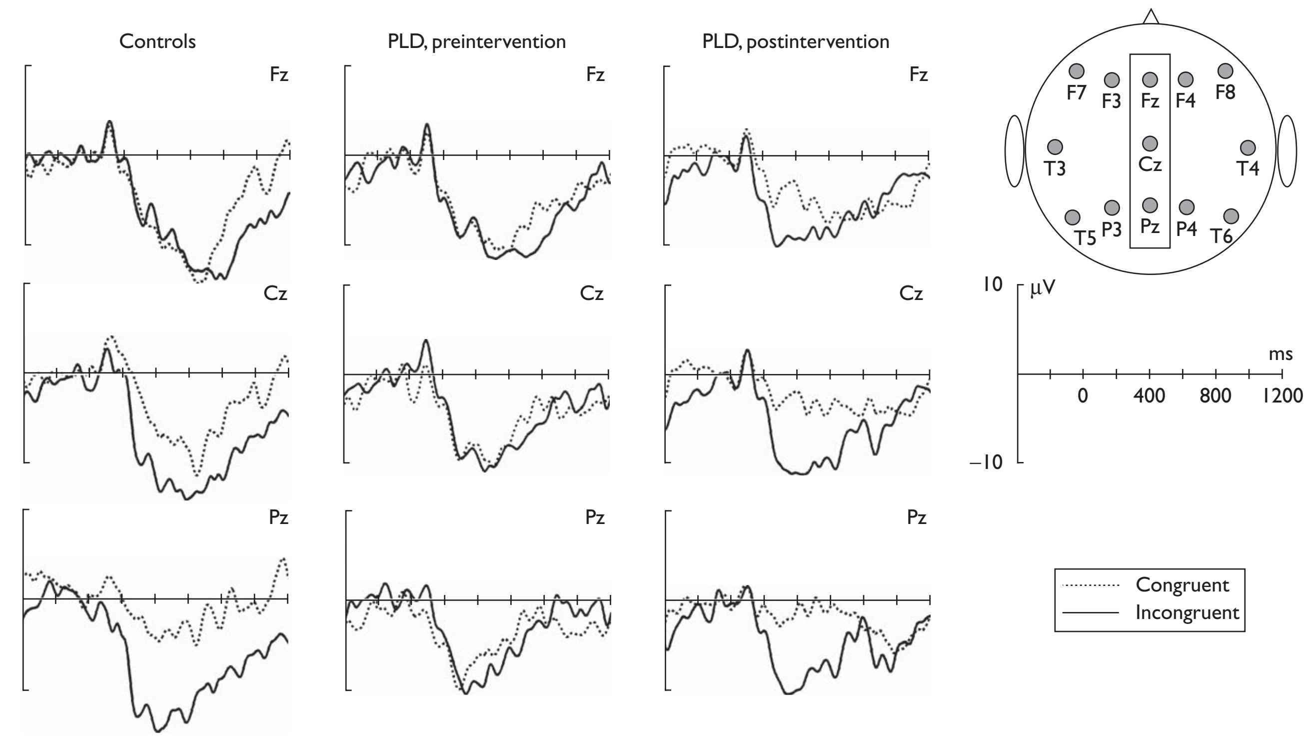
TD versus PLD pre-NBLI

As shown in Fig. 1, significant between-group differences in the semantic effect were noted at sites Cz [$F(1,13) = 3.9$; $P = 0.07$] and Pz [$F(1,13) = 6.5$; $P = 0.02$]. A significant semantic effect was present in the TD group at Cz [$F(1,6) = 10.4$; $P = 0.02$] and Pz [$F(1,6) = 20.3$; $P < 0.01$]. No semantic effect reached significance for the PLD group [$F(1,7) < 1.1$; $P > 0.32$]. These results indicate that before intervention, the group of children with PLD lacked the semantic effect that was observed for TD controls over centro-parietal sites.

Pre–post-NBLI changes

The within-group semantic effects were examined before and after NBLI. Significant effects of Time were observed at Cz [$F(1,7) = 12.5$; $P < 0.01$] and Pz [$F(1,7) = 5.7$; $P = 0.05$]. A significant semantic effect was present post-NBLI at Cz [$F(1,7) = 13.1$; $P < 0.01$] and Pz [$F(1,7) = 23.1$; $P < 0.01$]. Tests conducted separately on congruous and incongruous responses showed a significant effect of Time for the congruous condition at Cz [$F(1,7) = 10.9$; $P = 0.01$] and Pz [$F(1,7) = 9.8$; $P = 0.02$], indicating a pre–post-NBLI amplitude decrease. No Time effect was observed for

Fig. 1



Grand averaged event-related potentials of typically developing (left column) and primary language disorder (PLD; two right columns) groups elicited at midline sites by terminal congruous/incongruous words.

the response to incongruous stimuli [$F(1,7) < 0.4$; $P > 0.42$]. These results indicate the presence of a semantic effect after the completion of NBLI, which is because of an absolute mean amplitude decrease in the congruous condition.

Such changes could reflect the influence of repeated testing more than the effects of intervention. To investigate this possibility, we examined the semantic effects for the group that received NBLI after a waiting period. No significant semantic effects were observed in this group at study onset [$F(1,4) < 4.2$; $P > 0.11$] or after the 6-week no-treatment wait [$F(1,4) < 1.27$; $P > 0.32$]. In contrast, a significant semantic effect was observed after NBLI at Cz [$F(1,4) = 6.4$; $P = 0.06$] and Pz [$F(1,4) = 10.1$; $P = 0.03$]. The finding of no significant gains at the second testing increases the likelihood that semantic effects observed after NBLI are related to intervention rather than task experience.

Correlations between brain responses and behavioral performance

Apparent changes in the semantic effect were largest and most consistent at Pz. To limit the type 1 error, correlational analyses involved only the semantic effect at this site. The first analysis correlated pre-NBLI semantic effects with NLAI, NC, and ON, using combined data from TD controls and PLD. One outlier needed to be excluded. This test showed that larger N400 effects were associated with better narrative skills (NLAI = 88.1–1.81 × semantic effect, Pearson's $r = -0.58$, $P = 0.03$; NC = 25.1–0.45 × semantic effect, $r = -0.53$, $P = 0.05$; ON = 35.0–1.35 × semantic effect, $r = -0.54$, $P = 0.05$). A second analysis investigated the relationship between the changes in semantic effects from pre-NBLI to post-NBLI and the change in NLAI, NC, and ON over the same period. These correlations were not statistically significant ($|r| < 0.35$, $P > 0.39$).

Discussion

Before interventions, brain responses of children with PLD showed a prominent negativity distributed over frontal, central, and parietal areas, peaking at approximately 450 ms and being elicited by both congruous and incongruous sentence-terminal words. Although children with PLD performed similarly to TD controls in identifying semantically correct and incorrect words, their ERPs lacked the semantic effect that was otherwise present in TD controls. These results are consistent with findings reported by Sabisch *et al.* [7] and suggest that the task places larger semantic demands on the PLD participants even when presented with congruous words. After completion of the language intervention program, PLD participants showed significant changes in their brain responses, leading to the presence of the typical incongruous–congruous difference. The emergence of the semantic effect was because of a reduction in the amplitude of the N400 response to congruous words.

The change we observed in the N400 response after NBLI could have several explanations. First, intervention could have directly facilitated the processing of verbal input required to form and integrate various types of representations (e.g. lexical, grammatical, and discourse). This type of effect would have reduced the amount of effort required to integrate congruous words with the preceding context. The significant behavioral gains and the correlation between the amplitude of the N400 semantic effect and NLAI pre-NBLI support this possibility. In contrast, the absence of significant gains in grammatical measures indicates that grammatical aspects of language processing were not major factors underlying the electrophysiological changes. Moreover, gains in the neurophysiologic effect were not correlated to behavioral gains after NBLI. This limits confidence that changes in N400 response were a neurophysiologic analog to language development (as characterized by gains in NLAI) associated with NBLI.

Second, the intervention could have affected the processes underlying language skills, such as phonological short-term memory [15] or attentional skills [16]. Third, despite our observation that five participants showed no gains in the N400 semantic effect over the 6-week waiting period, we cannot rule out completely the possibility that gains we observed after NBLI also reflect influences of repeated testing.

Our participants with PLD, who had weak receptive and expressive language skills, made gains in both NC and ON after NBLI. Owing to the small sample size, a more specific relationship between the semantic effect and the receptive versus expressive deficits could not be assessed in this study. Our findings, however, may set the stage for additional investigations aiming to elucidate this aspect, and to test whether the effects in participants with SLI versus NLI display any divergent patterns.

Conclusion

Results of this study indicate that 6 to 8-year-old children with language impairment lack the N400 effect that is observed in TD children, presumably reflecting weaker semantic integration competence. Completion of an NBLI program, which placed heavy demands on semantic integration abilities, was associated with significant changes in the brain activity profile. A decrease in the response to congruous words and the presence of the semantic N400 effect after intervention are possible signatures of an improvement in lexical–semantic processing.

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