Spatiotemporal Neural Dynamics of Word Understanding in 12- to 18-Month-Old-Infants

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Learning words is central in human development. However, lacking clear evidence for how or where language is processed in the developing brain, it is unknown whether these processes are similar in infants and adults. Here, we use magnetoencephalography in combination with high-resolution structural magnetic resonance imaging to noninvasively estimate the spatiotemporal distribution of word-selective brain activity in 12- to 18-month-old infants. Infants watched pictures of common objects and listened to words that they understood. A subset of these infants also listened to familiar words compared with sensory control sounds. In both experiments, words evoked a characteristic event-related brain response peaking ~400 ms after word onset, which localized to left frontotemporal cortices. In adults, this activity, termed the N400m, is associated with lexico-semantic encoding. Like adults, we find that the amplitude of the infant N400m is also modulated by semantic priming, being reduced to words preceded by a semantically related picture. These findings suggest that similar left frontotemporal areas are used for encoding lexico-semantic information throughout the life span, from the earliest stages of word learning. Furthermore, this ontogenetic consistency implies that the neurophysiological processes underlying the N400m may be important both for understanding already known words and for learning new words.

Keywords: language development, magnetoencephalography, MRI, N400m

Introduction

Although lesions of Broca's and Wernicke's areas have long been known to produce aphasia in adults, it is unknown whether the developing linguistic skills of the child rely on these same left frontotemporal networks. Since lesions of these areas in early childhood have little effect on language development, it has been suggested that other brain areas may be necessary for learning language (Bates 1999). For example, it has been suggested that right hemisphere and anterior frontal regions are initially critical for language (Thal et al. 1991) and that classical language areas of adulthood become dominant only with increasing linguistic experience (Mills et al. 1993, 1997; Elman et al. 1996). Alternatively, the same areas may be involved in language across the life span, but the greater plasticity of the infant brain may permit complete recovery of language after left frontotemporal lesions because other areas are capable of assuming their functions (Staudt et al. 2002). Distinguishing between these alternatives has not been possible due to the minimal evidence for where language

is processed in the developing brain (Dehaene-Lambertz et al. 2002, 2006; Redcay et al. 2008; Grossman et al. 2010). Specifically, it remains unclear when mature language processes become functional in the brain and to what extent the neuroanatomical networks supporting early language resemble adult systems.

In addition to deficit-lesion correlations, language systems can be localized by probing the activation of different cortical areas to language stimuli. These methods, notably positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), localize language processes in areas generally consistent with lesion studies (Binder et al. 1997; Indefrey and Levelt 2004). However, these hemodynamic techniques are not easily applied to infants and have only been attempted in either very young populations (<3 months) when language abilities are primitive (Dehaene-Lambertz et al. 2002, 2006) or in sleeping or sedated populations when language functions are compromised (Redcay et al. 2008). Here, we used magnetoencephalography (MEG) in combination with high-resolution structural magnetic resonance imaging (MRI) to estimate the spatiotemporal distribution of word-selective brain activity in 1-year-old infants. Specifically, we used this noninvasive technique, termed dynamic statistical parametric mapping (dSPM) (Dale et al. 2000), to determine if the spatiotemporal dynamics of lexico-semantic processing typical of adults are already present during early stages of word learning.

The neural signature of adult lexico-semantic processing has been widely measured as the N400 event-related potential component (Kutas and Hillyard 1980). Peaking approximately 400 ms after word onset, the N400 is evoked by words in multiple sensory modalities and is attenuated when integration of the word into the cognitive context is facilitated by a wide variety of information. For example, the N400 is attenuated to a given word by previous presentation of the same word ("repetition priming") or a semantically related stimulus ("semantic priming") (Kutas and Federmeier 2000). The cortical currents that underlie the N400 also produce a magnetic field, recorded by MEG as the N400m. Although it is difficult to localize the generators of the N400 from scalp EEG in adults, the N400m has been localized in several studies using dSPM (Marinkovic 2004) to the left anteroventral temporal, posterosuperior temporal, and posteroventral prefrontal cortices (Halgren et al. 2002). Language tasks evoke hemodynamic activation in these areas (Indefrey and Levelt 2004), and intracranial local field potentials have steep voltage gradients, with local polarity inversions, demonstrating local generation and validating dSPM accuracy (Smith et al. 1986;

Halgren et al. 1994a, 1994b; Nobre et al. 1994; Guillem et al. 1995). Degeneration in the anterior temporal lobe is associated with semantic dementia (Hodges et al. 1992), posterosuperior temporal lesions are associated with Wernicke's aphasia and lesions of the posteroventral prefrontal cortex with Broca's aphasia (Goodglass 1993). Thus, in adults, dSPM allows one to use the N400m to probe lexico-semantic activity in the same distributed network of major language areas that are identified with lesions, fMRI, PET, and intracranial recordings.

To determine if 1-year-old infants use these same functional lexico-semantic networks for processing word meaning, we measured their MEG response to spoken words in 2 separate experimental conditions (Fig. 1A,B). Auditory words were selected that infants understood, according to parental report. MEG was recorded in a quiet magnetically shielded room as infants sat in a child-size chair situated below the MEG sensors (Supplementary Fig. S1). We then acquired an MRI while the infants slept naturally in the scanner. Their cortical surfaces were reconstructed and used to constrain possible generators for dSPM source estimation.

Materials and Methods

Participants
Data from 12 typically developing infants ages 12–18 months (mean age= 15.2 months ± 2.4, 5 males) are presented here. All infants had monolingual English exposure, were born full-term (>39 weeks), and had no known neurological or developmental impairments. Language abilities were assessed with the MacArthur-Bates Communicative Developmental Inventories (CDI) (Fenson et al. 1994) (Supplementary Table 2). CDI measurements could not be obtained for Subject 9, but this subject was considered typically developing. Written parental consent was obtained for all infant subjects. This study was approved by the UCSD Institutional Review Board (Project #070254) and was conducted according to the principles expressed in the Declaration of Helsinki.

Experimental Design

Stimuli
Parents rated 100 words selected from the CDI using a modified Word Rating Checklist (0-Doesn't Know to 4-Very Familiar) (Mills et al. 1993). Thirty highly rated words (3-Familiar or 4-Very Familiar) were then selected for each child for presentation during the experiment (Supplementary Table 1). Word stimuli were simple nouns spoken in an infant-directed manner. Sound files (mean duration = 0.72 s ± 0.12) were digitized at 16 kHz and normalized to an average intensity of 65 dB.

Auditory Words Versus Complex Noise
Infants ($n = 4$) listened to a series of words pseudorandomly alternated with signal correlated noise (SCN) sounds that served as an auditory sensory control (Fig. 1A). Using Praat software (www.praat.org), each SCN stimulus was generated by applying the extracted amplitude envelop of a word to a pink noise sound, that was effectively band-pass filtered to maintain the same overall frequency spectrum as the given word. This process results in a complex auditory stimulus that maintains the time-varying amplitude envelop and average spectral power of a word (Rodd et al. 2005). A matching SCN control stimulus was constructed for each word, and the MEG averages were constructed from these matching pairs—if the MEG evoked by a particular word needed to be rejected due to an artifact from the word average, then the corresponding SCN was removed from the SCN average and vice versa. Sounds were presented in 3 blocks of 60 trials each (30 words, 30 SCN).
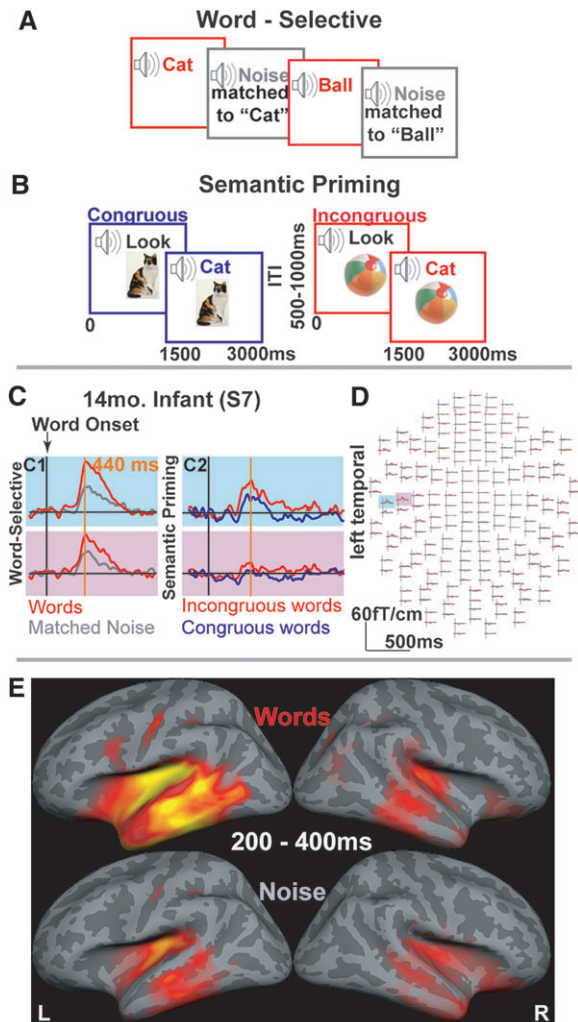

Figure 1. Adult-like N400m brain responses of 1-year-old infants. (A) Task used to demonstrate responses selective for words as compared with matched auditory controls. (B) Task used to demonstrate semantic priming by comparing the response with words preceded by congruous versus incongruous pictures. (C) Averaged single channel event-related fields from a representative 14-month infant. (C1) Word-selective activity (words > matched noise) peaks in left temporal channels at ~440 ms. The average field strength in the 200 ms time window (350–550 ms) surrounding this peak in the displayed channels was measured on each trial ($n = 106$) and compared between congruous and incongruous conditions using a t-test ($t_{105} = 3.25$, $P < 0.002$ [blue channel]; $t_{105} = 2.05$, $P < 0.04$ [purple channel]). (C2) Semantic priming of brain activity in the same subject and sensors. Like the difference between words and noise (incongruous > congruous), the semantic effects were significant when compared across trials ($n = 82$) in the different conditions during the 200-ms period surrounding peak activity ($t_{81} = 2.13$, $P < 0.04$ [blue channel]; $t_{81} = 2.88$, $P < 0.005$ [purple channel]). (D) Whole-head MEG sensor array of the response selective for words as compared with noise, with color coding to indicate the left temporal gradiometers where the largest differential responses to word selective and semantic priming are observed for the individual subject shown in (C). (E) Group average dSPM activity ($n = 4$) to words and noise 200–400 ms following word onset. Words exhibit greater activity in left frontotemporal regions than noise. Color indicates signal-to-noise relative to prestimulus baseline (full red at sqrtF = 4.3, full yellow at sqrtF = 6.3). Subject number (S7) corresponds to subject 7 listed in Supplementary Table 2.

Semantic Modulation of Auditory Words
Semantic context was manipulated by presenting pictures and auditory word pairs whose meanings were either congruously (picture of a cat followed by the word "cat") or incongruously (picture of a ball followed by the word cat) matched (Fig. 1B). To control for sensory-perceptual differences between conditions, each picture and each word appeared

in both congruous and incongruous conditions. The initial presentation of each word was congruous for half the words and incongruous for the other half. Again, the MEG averages were constructed from these matching pairs—if the MEG evoked by a particular word in the congruous condition needed to be rejected due to an artifact from the congruous word average, then the MEG evoked by same word was removed from the incongruous word average and vice versa. Each trial began with the simultaneous presentation of a picture stimulus and the orienting stimulus sound "Look" (duration = 0.52 s). At 1.5 s after picture onset, an auditory word was presented (picture duration = 3 s). Infants viewed up to 3 blocks (180 total trials; 60 trials per block, 30 trials per condition). Trials were presented pseudorandomly, such that congruous–incongruous conditions for a given word did not occur sequentially. Incongruous picture–word pairs were varied across blocks to limit the effects of habituation. Incongruous words were chosen to differ from the correct word in their initial phonemes (e.g., "bottle" presented after a picture of a dog). We controlled for potential differences in infants' individual familiarity with the visual objects used to semantically prime familiar auditory words by requesting that parents practice with an individualized training picture booklet for 5–10 min per day, 5 days prior to the MEG scan.

Neuroimaging Procedures

MRI Acquisition
Image acquisitions included a conventional 3-plane localizer, a calibration scan, and 2 T_1-weighted 3D structural scans (time echo = 2.8 ms, time repetition = 6.5 ms, time to inversion = 600 ms, flip angle = 12°, bandwidth = 31.25 Hz/pixel, field of view = 25.6 cm, matrix = 256 × 162, slice thickness = 1.2 mm). MR scans were obtained on a GE 1.5-T EXCITE HG. Scanning began once the child fell naturally to sleep in the scanner. Noise-canceling headphones (Innomed) were used to minimize and protect infants from scanner sounds.

MEG Recordings
MEG was recorded using a 306-channel Elekta Neuromag Vectorview system in a magnetically shielded room (IMEDCO-AG). Four head positioning indicator coils were gently affixed to the infant's head. The main fiduciary positions including the nasion, left and right preauricular, and additional head points were digitized to allow for later registration with MR images (Hämäläinen 1991). During the MEG session, infants sat upright in a booster seat with their heads positioned beneath the helmet-shaped dewar (Supplementary Fig. S1). Foam padding was placed inside the dewar to stabilize the infants' heads and minimize movement. Scans with head translation between the first and last block >3 cm were excluded (Supplementary material). Sampling rate was 2000 Hz, with minimal filtering (0.1 to 200 Hz). An experimenter was always present in the MEG room during scanning and initiated trials manually when the infant's attention was directed toward the screen.

Data Processing and Analysis

MEG Preprocessing
After low-pass filtering (50 Hz), visually identified bad channels and trials with gradiometer signals >3000 fT/cm were removed from analyses, as were poorly attended trials or trials containing blink artifacts, indentified by visual inspection of magnetometer channels. Electrocardiographic artifacts were removed using independent component analysis (Delorme and Makeig 2004). Sensory confounds were prevented by comparing the responses with words with the responses to SCN constructed from those same words. Similarly, the responses to words presented with a congruous picture were compared with the responses to the identical words presented with an incongruous picture. For all experiments, infants had an equal number of trials per condition. Each subject had a minimum of 20 trials per condition (71.5 ± 26.7 trials per condition for words vs. noise; 52.2 ± 21.2 for semantic priming). Data were epoched from –200 to 1200 ms relative to stimulus onset (words vs. noise) or –200 to 1500 ms relative to onset of the auditory word (semantic priming).

Source Estimation from MEG
Cortical sources of MEG activity were estimated using a noise-normalized linear inverse technique (dSPM; Supplementary material) (Dale et al. 2000), previously employed in adult studies of the N400 (Dhond et al. 2001, 2003, 2005, 2007; Halgren et al. 2002; Marinkovic et al. 2003; Marinkovic 2004; Leonard et al. 2010). First, the cortex was reconstructed from each infant's MRI and tiled with ~5000 dipoles were constrained to lie in the cortical surface reconstructed from each individual infant's MRI and calculating the projection from each patch to the sensors using the boundary element method (BEM; Oostendorp and Van Oosterom 1992). Dipole power was estimated using a minimum norm approach (Dale and Sereno 1993; Liu et al. 1998, 2002) and then normalized to baseline noise (Liu et al. 2002). These dSPM maps were averaged across subjects after aligning their cortical surfaces, resulting in dynamic activation maps which can be interpreted as estimates of the of signal-to-noise at each point on the cortical surface, and thus analogous to the "z-score maps" often displayed in fMRI analyses (Friston et al. 1999; Dale et al. 2000). Using this measure, the P values in the displayed maps were all less than 0.05.

ROI Analysis
dSPMs were calculated for each subject (n = 12 infants; n = 7 adults), and then averaged onto the aligned cortical surfaces. Based upon the a priori prediction that average peak N400m-like activity would occur between 350 and 550 ms following word onset, a 50-ms temporal window surrounding the largest peak (500–550 ms) in infant group time course activity was selected for statistical analysis in various regions of interest (ROIs). ROIs were selected based on a priori predictions that N400m generators would be located in posteroventral frontal and anterior temporal regions. Specific ROI locations were determined by visual inspection of group average dSPM maps of word activity (350–550 ms) without regard to condition. For a given ROI, a within-subjects 2-tailed, paired t-test was performed on the mean activity obtained from the 50-ms time window for each condition. This approach is quite conservative since it does not allow for inconsistent spatial distribution or latency across subjects. All statistical analyses are uncorrected for multiple comparisons.

Leadfield Analysis
Leadfield analysis provides a means of confirming the origin of the word-selective MEG responses estimated by dSPM but without a priori assumptions concerning the number, focality, or correlation of sources (Halgren et al. 2010). The "cortical leadfield" of a particular sensor is the area of cortex that projects activity to it and is a biophysical calculation assuming only that the sources are parallel to the apical dendrites of pyramidal cells. Leadfields were calculated using BEM and a tessellation of the individual infant's cortical surface with ~300 000 vertices (Oostendorp and Van Oosterom 1992). Leadfield analyses were performed on the 3 gradiometers that exhibited the largest differential responses to semantic priming of words in an 18-month infant during the 350-550 ms time window (Fig. 4). Significance of these responses within the single channel and infant was tested with a 2-tailed, paired t-statistic between conditions, on the mean activity during the 350-550 ms time window measured on each trial (n = 60).

Semantic Modulation of Auditory Words (Adults)
The experimental task was exactly the same as the task performed in infants, with the sole exception that adults were presented a total of 100 unique words rather than the 30 that were presented to the infants. The auditory word stimuli were paired with pictures across 4 blocks (25 congruous and 25 incongruous trials per block) for a total of 200 trials pairs. Trial timing was the same for infant and adult experiments. Auditory and picture stimuli were the same as those presented to infants. Adults also had an equal number of trials per condition (96.7 ± 3.64 trials per condition). MEG recordings were acquired in the same manner as infants. Trials were eliminated which were contaminated by blink artifacts as identified by the Electrooculogram. MEG processing and dSPM source estimation were the same as described above. Subjects (n = 7) were right-handed monolingual adults (mean age = 28.6 years; 4 males, 3 females) and gave informed consent.

Results

In our first study, 4 infants listened to words randomly intermixed with SCN sounds constructed to match each of the stimulus words (Fig. 1*A*). Representative MEG responses from a 14-month infant appeared larger in amplitude to words than SCN at ~440 ms (Fig. 1*C*1). This word-selective activity occurred primarily within gradiometer channels over the left temporal lobe and posteroventral prefrontal cortex (Fig. 1*D*). Since gradiometers are mainly sensitive to the directly underlying cortex, this pattern suggests generation within frontotemporal cortices. This inference was confirmed with source localization using dSPM in each subject, which was then averaged across subjects on the cortical surface. Words evoked greater activity in the left temporal, insular, and posteroventral frontal cortices (Fig. 1*E*), at a latency (200–400 ms) consistent with when adult N400m activity differentiates words from earlier stimulus evoked sensory activity (Sekiguchi et al. 2001). Since the time-varying acoustic features of each stimulus word were precisely matched in the corresponding SCN stimulus, this comparison allowed us to isolate brain activity that reflects lexico-semantic as opposed to sensory processes. It is important to note that acoustic differences between words and other types of control stimuli (e.g., unknown words and backwards speech) would have prevented such inferences because lexical and sensory differences would have been confounded.

While this activity is in the same cortical location and latency range as the adult N400m, the comparison of words and noise only shows that it is word selective. An additional critical feature of the adult N400m is that it is strongly modulated by semantic and repetition priming. We used pictures to semantically prime the auditory word response in 12 infants (Fig. 1*B*). Each word was presented twice, once preceded by a picture of the same object and once by a picture of a different object (Supplementary Table 1). Since the word stimuli in the congruous and incongruous conditions were identical, any difference between them must be due to semantic priming. At the single subject level, it was possible to observe event-related MEG responses to congruous words that were reduced by semantic priming (Fig. 1*C*2). This semantically modulated word activity occurred within the same left temporal MEG channels as the word versus noise effect (Fig. 1*C,D*). We also explored repetition priming in a subset of these subjects to obtain additional evidence that word-selective activity shared characteristic modulations with the adult N400 (Supplementary Fig. S2). Finally, since this specific semantic priming task has not been previously performed in adults during MEG recordings, this experiment was repeated in adults (*n* = 7) to confirm that our experimental infant paradigm would evoke a typical N400m response in adults. Similar to infants, adult subjects showed a greater amplitude response to semantically primed incongruous words in these same left temporal MEG channels (Fig. 3*A,B*).

The average cortical distribution of differential activation to incongruous versus congruous words was estimated with dSPM to be concentrated mainly to left posteroventral prefrontal cortex, perisylvian, and anterior temporal lobe regions (Fig. 2), with weaker activation in 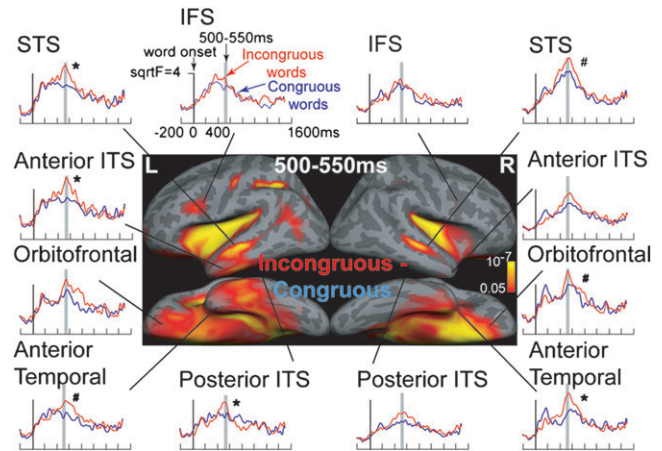homologous right hemisphere sites. These locations correspond closely to previously established dSPM (Dhond et al. 2001, 2003, 2005, 2007; Halgren et al. 2002; Marinkovic et al. 2003; Marinkovic 2004; Leonard et al. 2010)

Figure 2. Estimated localization of N400m activity modulated by semantic priming in 12- to 18-month-old infants. Center: Group average dSPM (*n* = 12) to incongruous minus congruous words from 500 to 550 ms (centered on the largest peak in the group time course activity), displayed on the cortical surface (dark gray = sulci, light gray = gyri). In the left hemisphere, activity is estimated to anterior and ventral temporal regions, insula, planum temporal, frontal operculum, inferior frontal sulcus, and orbital cortex. Right hemisphere activity is more restricted. Color indicates signal-to-noise relative to prestimulus baseline (full red sqrtF = 1.2, $P < 0.05$, full yellow sqrtF = 2.6, $P < 10^{-7}$, degrees of freedom = 36). Surround: Average time courses for the estimated noise-normalized dipole strength to incongruous (red) and congruous (blue) words in 6 bilateral ROIs. The amplitude of the time course to congruent and incongruent words from 500 to 550 ms was determined in each subject and compared with a paired *t*-test. Time courses with a * indicate regions where a significant difference was found (# = trend). IFS, inferior frontal sulcus; STS, superior temporal sulcus; ITS, inferior temporal sulcus.

and intracranial (Smith et al. 1986; Halgren et al. 1994a, 1994b; Nobre et al. 1994; Guillem et al. 1995) estimates of adult N400m activity as well as dSPM estimates of activity evoked using the semantic priming task designed for infants (Fig. 3*C*). Furthermore, infant dSPM estimates of semantically modulated activity (incongruous–congruous) in infants were found to be significantly correlated across cortical locations with adult dSPM estimates in both left (Pearson's $r_{149,995} = 0.61$, $P < 10 \times 10^{-8}$) and right hemispheres (Pearson's $r_{149,926} = 0.77$, $P < 10 \times 10^{-7}$) during the time window from 500 to 550 ms (Supplementary material).

In order to confirm the reliability of semantic priming effects across all subjects, more rigorous statistical tests were performed on 6 bilateral cortical ROIs. First, a 2-way repeated measures analysis of variance (ANOVA) was performed for each bilateral ROI, within-subjects factor of condition (congruent and incongruent) and between-subjects factor of group (infant and adult). A significant main effect of condition was obtained in all left hemisphere ROIs: Left superior temporal sulcus ($F_{1,17} = 10.64$, $P < 0.005$), left anterior inferior temporal sulcus ($F_{1,17} = 8.414$, $P < 0.01$), left posterior inferior temporal sulcus ($F_{1,17} = 9.26$, $P < 0.007$), left anterior temporal pole ($F_{1,17} = 9.53$, $P < 0.007$), left inferior frontal sulcus ($F_{1,17} = 8.96$, $P < 0.008$), and left orbitofrontal cortex ($F_{1,17} = 9.92$, $P < 0.018$). There was no significant effect of condition found in right hemisphere ROIs. No significant main effects for group were observed in right or left hemisphere ROIs ($F_{1,17}$ varied from 0.01 to 2.72). In the right hemisphere, a significant interaction (group × condition) was observed in the anterior temporal pole ($F_{1,17} = 7.23$, $P < 0.016$). The Greenhouse–Geisser Correction for repeated measure was applied to all measures with more than 1 degree of freedom.

To explore these overall effects, we also performed within-subjects 2-tailed paired t-tests to confirm that both infant and adults demonstrated significant incongruous > congruous semantic priming effects. For infants, these tests revealed significant incongruous > congruous semantic effects in the left superior temporal sulcus (t_{11} = 2.46, P < 0.03), anterior inferior temporal sulcus (t_{11} = 2.76, P < 0.02), and posterior inferior temporal sulcus (t_{11} = 2.97, P < 0.01), with a trend in the temporal pole (t_{11} = 2.07, P < 0.06; Fig. 2). In the right, only the anterior temporal pole demonstrated an incongruous > congruous significant response (t_{11} = 2.77, P < 0.02), with trends in the right superior temporal sulcus (t_{11} = 2.15, P < 0.06) and orbitofrontal cortex (t_{11} = 1.94, P < 0.08) (Fig. 2). ROI analysis of the adult response for these same 6 bilateral ROIs revealed a similar pattern (Fig. 3C). Significant incongruous > congruous semantic effects were observed in the left inferior frontal sulcus (t_6 = 2.58, P < 0.04), left temporal pole (t_6 = 2.63, P < 0.04), and left orbitofrontal regions (t_6 = 2.41, P < 0.05), with a trend in the superior temporal sulcus (t_6 = 1.99, P < 0.09). No significant differences were observed in homologous right hemisphere regions.

Since dSPM has only been validated in adults for the N400, we also used a sensor-based approach to verify that our source estimates were reasonable. For these leadfield analyses, we first identified the 3 gradiometer channels exhibiting the largest semantic incongruity effect in an individual subject (Fig. 4B) and found that the activity in these sensors showed highly significant differences between congruous and incongruous words between 350 and 550 ms Channel 1 (t_{59} = 3. 76, P < 0.0004), Channel 2 (t_{59} = 2.06, P < 0.04), and Channel 3 (t_{59} = 2.87, P < 0.006). We then calculated the relative strength of the projection from each cortical location to these sensors, finding that only the left posterolateral temporal cortex projects significantly to the responsive sensors (Fig. 4). Although these sensors are weakly sensitive to more distant areas, sensors over these distant areas did not exhibit strong activity in Figure 4A1–3. This provides additional evidence, independent of dSPM estimations, that the largest semantic priming responses are highly likely to arise in the left posterior temporal cortex. In combination with representative single-subject MEG data, group dSPM estimates, and ROI analyses, these leadfield calculations provide converging evidence that the evoked brain responses of 1-year-old infants share spatial, temporal, and cognitive characteristics of the adult N400m.
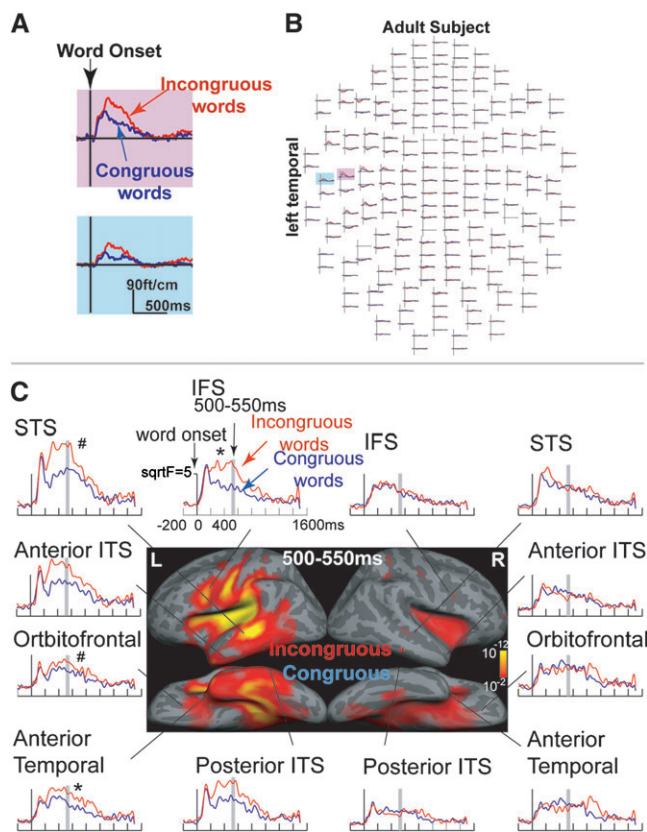
Figure 3. MEG recordings from adults during the semantic priming task developed for infants. (*A*) Averaged single channel event-related fields from a representative adult during the semantic priming task shown in Figure 1*A*. A sustained differential response (incongruous > congruous) is observed at a similar latency (350–550 ms) as infants, but the peak of the differential response may occur earlier for adults. This differential response is significant across trials for the 200-ms time window (350–550 ms) (P < 0.00001 [purple channel]; with a trend in the [blue channel] P < 0.08). Two-way t-test, P < 0.05, degrees of freedom = 98. (*B*) Whole-head MEG sensor array recordings of the semantic priming response in the same adult. Color coding indicates the left temporal gradiometer channels that correspond to where differential word selective, semantic, and repetition priming responses were observed in infants (Figs 1*C* and 4*B*, Supplementary Fig. S2). (*C*) Center: Adult average dSPM (*n* = 7) to incongruous minus congruous words at the same latency (500–550 ms) as the infant group response (Fig. 2) displayed on the cortical surface (dark gray = sulci, light gray = gyri). Similar to infants, sources generating the differential semantic priming response are estimated in adults to left posterior prefrontal, perisylvian, and anterolateral temporal regions, with weaker activation in homologous right hemisphere sites. Color indicates signal-to-noise relative to prestimulus baseline (full red at sqrtF = 1.7 corresponding to P < 10^{-2}, full yellow at sqrtF = 3.5, P < 10^{-12}). Surround: Average time courses for the estimated noise-normalized dipole strength to incongruous (red) and congruous (blue) words in the same 6 bilateral ROIs used for infant analyses. The amplitude of the time course to congruent and incongruent words from 500 to 550 ms was determined in each adult subject and compared with a paired t-test. Time courses with a * indicate regions where a significant difference was found (# = trend). IFS, inferior frontal sulcus; STS, superior temporal sulcus; ITS, inferior temporal sulcus.
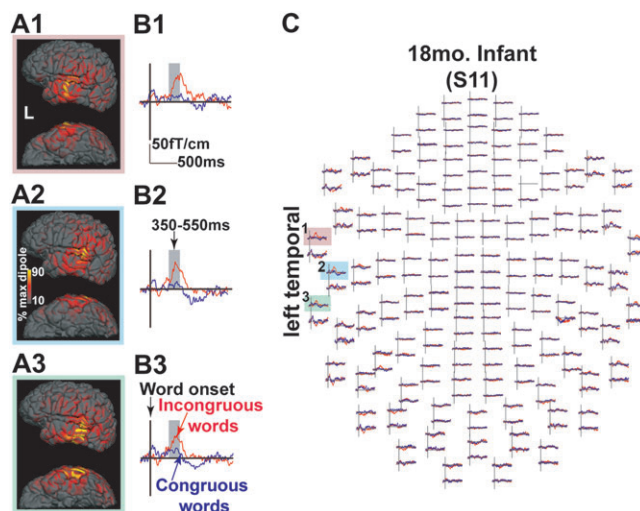
Figure 4. Cortical leadfields for left temporal gradiometers with the largest semantic priming response from an 18-month infant. (*A*) The cortical sensitivity of a given sensor is displayed on the pial surface. (*A1–3*) Channels are strongly sensitive to left posterior temporal regions and weakly to other perisylvian regions. Dipoles projecting 90% as strongly as strongest dipole are yellow; red dipoles project 50%, gray project <10%. (*B*) Significant semantically modulated activity (incongruous [red] > congruous [blue]) occurs between 350 and 550 ms. (*C*) The entire gradiometer array, showing that these channels have the largest differential responses to semantic priming of words. Color coding is consistent across all figures. Subject number (S11) corresponds to subject listed in Supplementary Table 2.

Discussion

Taken together, these results imply that the basic neural mechanism used to encode lexico-semantic information is established during infancy and operates within similar cortical structures throughout the life span. Our evidence for left frontotemporal language processes during infancy implies that early lesions of these areas are followed by a transfer of dominant responsibility for language to the right hemisphere rather than the right hemisphere being dominant at the earliest stages of normal language development. Although differential activity has previously been observed in the infant EEG to words preceded by incongruous versus congruous pictures (Friedrich and Friederici 2005), the relation of this response to the adult N400 is uncertain due to differences in timing, polarity, and topography. Clear N400 activity, however, has been observed in school age children (Holcomb et al. 1992). Thus, the brain mechanisms for processing lexico-semantic information are likely quite stable, even in the face of significant structural brain changes during development (Giedd et al. 1999). The robust nature of N400 processes is further underscored by the fact that we observed significant group effects of semantically modulated word-selective activity at ages when language skills are widely variable (Fenson et al. 1994) (Supplementary Table 2).

Although the infant N400 latency, location, and task correlates clearly place it within the range of the adult N400, quantitative differences between adults and infants are still possible. Indeed, such differences are expected given the rapid changes during early childhood in the cortical areas generating the N400. The consistency of the N400 across development also does not rule out the possibility of significant developmental changes in the neural substrates of other language-related processes. Such changes have been identified in fMRI studies of older children and may be related more to speech production or associated strategic, attentional, and perceptual processes rather than lexico-semantic integration (Schlaggar et al. 2002; Brown et al. 2005). The presence of the N400 during infancy implies that it helps to form the neurophysiological context guiding the connections that are formed in this critical period.

The discovery of a fundamental lexico-semantic process present throughout the rapid burst of language acquisition permits this process to be quantified and thus related to behavioral and neural development and their disorders. For example, there is infant event related potential evidence to suggest that brain activity may be a useful predictor of later language outcome (Kuhl et al. 2008). There are also other infant EEG studies which suggest that brain activity patterns to words become increasingly left lateralized as infants' language abilities improve (Mills et al. 1993, 1997). Similarly, a recent dSPM study of bilingual adults suggests that the second language may evoke relatively more right-sided activity that declines as words become better known (Leonard et al. 2010). Thus, future dSPM studies could be used to examine whether brain activity becomes even more concentrated within left frontotemporal cortex as infants continue to learn new words. Such evidence would have important implications for addressing long-standing questions concerning how environmental and maturational processes interact with language, both in the developing and mature brain.

In the present study, we performed an additional experiment to determine whether our semantic priming task designed for infants would evoke a typical N400m in adult subjects (Fig. 3). This was found to be the case, and in addition, the spatiotemporal patterns of differential semantic activity appeared highly similar in infants and adults. This was quantified as the correlation coefficient in the spatial distribution of cortical activation patterns during the N400m between infants and adults. This was found to be about 0.7, which is highly significant. Conversely, when ANOVAs were performed which included data from congruous and incongruous conditions in both infants and adults, a main effect of age was never seen, whereas the effects of condition were very similar for both groups. The one case where a significant group by condition interaction was observed was due to the temporal pole showing a condition effect bilaterally in infants but only unilaterally in adults. In general, both infants and adults demonstrated significant differential semantic activity within left frontotemporal regions, but infants tended to show more differential activity in right hemisphere regions than were observed in adults (Figs 2 and 3). Despite these small differences, a significant relationship was observed between the spatial distribution of estimated sources of right hemisphere activity in infants and adults. It is also worth noting that differences due to semantic priming appeared to peak somewhat earlier in adults, a finding which is consistent with developmental studies of the N400 (Holcomb et al. 1992). These studies have reported a decrease in N400 latency of ~120 ms from their youngest children (5 year old) to adults (23 years). However, since factors such as task performance were not directly controlled between adults and infants in the present experiments, it is difficult to assess whether these slight timing and location differences actually represent real developmental differences in the location and speed of lexico-semantic information processing.

It is remarkable that infants, with small lexicons, who have barely begun to speak, seem to use a very similar neural process as adults to understand words, with comparable timing, cortical location, and presumed neuronal substrate. The neural process represented by the N400 has been most intensively studied in adults during word reading. Potential words are initially encoded in ventral occipitotemporal cortex at ~170 ms (McCandliss et al. 2003) and projected to the middle layers of frontotemporal association cortices by ~200 ms. The N400 follows as a slow depolarization of apical dendrites of pyramidal cells in more anterior frontotemporal cortices, in layers that receive widespread associative inputs (Halgren et al. 2006). These physiological processes appear to reflect the recognition of a potential lexical element, followed by its integration with the current mental representation of the environment. If this lexico-semantic integration is facilitated by recent experience, via repetition or semantic priming, then the integration will proceed more quickly and the N400 will be attenuated, as in the current experiment. However, if the potential lexical element is unfamiliar, for example, a pronounceable nonword, the N400 is still triggered, at maximum amplitude. Thus, the N400 appears to reflect an optimal modulatory state for semantic integration of potential lexical elements within a given context; if the word is already known then preexisting associations will be activated leading to evolution of the semantic context; if the word is unknown, then the associations will lead to contextual learning of its meaning (Halgren 1990).

Since, in this view, the N400 does not depend on preexisting associations, it can be fully expressed before a significant vocabulary has developed in infants. However, this model does require the early development of a mechanism for selecting and segmenting potential words from the ongoing auditory stream. Indeed, both behavioral and neurophysiological evidence suggest that by ~7–8 months, infants both selectively listen to human voices (Grossman et al. 2010) and detect words based on the statistical regularities present in speech (Saffran et al. 1996). Additionally, it is also possible that the cellular maturity of prefrontal cortical regions observed in neuroanatomical studies (Petanjek et al. 2008) may support the rapid emergence of these neurophysiological processes. From the perspective of the young child learning her first language, all sounds that might be words need to be associated with salient aspects of the environment. The N400 may provide the necessary neurophysiological context for learning these lexico-semantic associations. As the vocabulary expands, the N400 increasingly is used for integrating known words with the semantic context, but its potential for facilitating contextual learning for new words is available throughout the life span.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

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