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Temporo-parietal connectivity uniquely predicts reading change from childhood to adolescence

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Abstract

Previous research has shown that left posterior middle temporal gyrus (pMTG) is a core node in the semantic network, and cross-sectional studies have shown that activation in this region changes developmentally and is related to skill measured concurrently. However, it is not known how functional connectivity with this region changes developmentally, and whether functional connectivity is related to future gains in reading. We conducted a longitudinal functional magnetic resonance imaging (fMRI) study in 30 typically developing children (aged 8–15) to examine whether initial brain measures, including activation and connectivity, can predict future behavioral improvement in a semantic judgment task. Participants were scanned on entering the study (time 1) and a follow-up period of 2 years (time 2). Character pairs were arranged in a continuous variable according to association strength (i.e. strong versus weak), and participants were asked to determine if these visually presented pairs were related in meaning. Our results demonstrated greater developmental changes from time 1 to time 2 for weaker association pairs in the left pMTG for the children (aged 8–11) as compared to the adolescents (aged 12–15). Moreover, the results showed greater developmental changes from time 1 to time 2 for weaker association pairs in connectivity between the pMTG and inferior parietal lobule (IPL) for the children as compared to the adolescents. Furthermore, a hierarchical stepwise regression model revealed that connectivity between the pMTG and IPL in weak association pairs was uniquely predictive of behavioral improvement from time 1 to time 2 for the children, but not the adolescents. Taken together, the activation results suggest relatively rapid development before adolescence of semantic representations in the pMTG. Moreover, the connectivity results of pMTG with IPL

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tentatively suggest that early development of semantic representations may be facilitated by enhanced engagement of phonological short-term memory.

Keywords

semantic; association strength; fMRI; longitudinal; connectivity

1. Introduction

Reading ability is associated with maturational changes in the brain, which in turn is essential for functioning in our daily life (Friederici, 2006; Johnson, 2011; Schlaggar and Church, 2009). Reading involves a rapid mapping between orthography and semantic representations in printed words. In neuroimaging studies, various regions (i.e. inferior frontal gyrus, angular gyrus, and middle temporal gyrus) have been indicated to be supportive to semantic processing (Booth et al., 2002; Chou et al., 2009; Wu et al., 2012). A longitudinal study using functional magnetic resonance imaging (fMRI) followed two developmental cohorts (children: age 8–11 and adolescents: age 12–15) during a semantic judgment task in Chinese. Using two cohorts allowed us to determine whether longitudinal changes differed between younger and older participants (McNorgan et al., 2011). Ours is the first study to determine the relationship of initial brain measures (i.e. brain activity, functional connectivity) to changes in skill of reading Chinese characters.

Chinese is different from alphabetical languages in the nature of the mapping between orthography and semantics at a mono-morphemic level. About 80% of Chinese characters are phonetic compounds (phonograms) that consist of a semantic radical and a phonetic radical (Zhou, 1978). The semantic radicals may provide a cue to the semantic category of the character (Ho et al., 2000). Thus, it is important to explore whether the unique linguistic features of Chinese influence developmental changes in the neural substrate for semantic processing.

Integration mechanisms have been investigated by examining the brain activation due to stronger versus weaker semantic association (Chou et al., 2009; Fletcher et al., 2000; Raposo et al., 2006). Previous fMRI studies in English have shown that stronger association results in greater activation in the left angular gyrus (AG, BA 39) (Chou et al., 2006a; Raposo et al., 2006). In addition, greater activation was observed in the left AG when participants were cued to be aware of the semantic features of the incoming word target (Cristescua et al., 2006). Several studies have proposed that the activation in the AG is related to the integration of multiple shared features between word pairs (Grossman et al., 2003; Koenig et al., 2005; Lee et al., 2015).

In contrast to greater activation in AG for stronger semantic association, processing weaker association has elicited greater activation in the left posterior middle temporal gyrus (pMTG, BA 21) and the ventral regions of left inferior frontal gyrus (IFG, BA 45/47). Several studies in English have shown that word pairs with weaker association strength result in greater activation in the left pMTG (Chou et al., 2006a; Wible et al., 2006). This region is often considered as a repository site for semantic knowledge (Binder et al., 2009). Greater

activation in this region for low association may result from a more extensive access to semantic representations in order to identify the distant relationships between words (Booth et al., 2007; Chou et al., 2009). Word pairs with weaker association strength also elicited greater activation in the left IFG. Greater activation in this region is likely related to difficulty of selecting relevant semantic features, as word pairs with weaker association share few semantic features (Fletcher et al., 2000). For weaker association pairs, in order to make appropriate semantic decisions, participants may engage greater activation in both pMTG and IFG.

Evidence from cross-sectional studies shows that developmental changes in semantic processing continue into early adulthood and it is associated with changes in the left IFG and MTG. Previous studies using a semantic association task have identified age-related changes in these two regions (Chou et al., 2009; Lee et al., 2011; Lee et al., 2015). Left IFG is proposed to be specialized for selecting relevant semantic features (Fletcher et al., 2000). Consistent with this notion, age-related increases in this region, particularly for the adolescents, may imply greater executive control needed to select relevant features. In addition, developmental changes in the MTG may reflect the elaboration of semantic knowledge with increasing numbers of semantic representations and stronger interconnections between these representations. Consistent with this argument, behavioral studies demonstrate that as vocabulary knowledge increases, the child's semantic system gradually matures due to a greater number of conceptual links (McGregor and Appel, 2002; McGregor et al., 2002). Although there is extensive support for the core role in the left MTG in developmental changes in semantic processing, a larger left-lateralized network for comprehension is also found to support age-related changes. An age-related increase in functional connectivity was found among the bilateral temporal regions, left IFG, and left AG in children using a narrative comprehension task (Karunanayaka et al., 2007; Schmithorst et al., 2007). These inter-connections in the semantic network may enable appropriate semantic representations to be accessed and integrated (Bokde et al., 2001; Turken and Dronkers, 2011). Taken together, previous work suggests that as children age they are more capable of maintaining conceptual knowledge in an organized state, using a flexible mechanism to retrieve/select relevant information and integrating relationships between these concepts (Blakemore and Choudhury, 2006; Crone et al., 2009).

In the current study, we were interested in developmental changes in the relationship between brain activation, connectivity, and behavioral improvement. Previous work shows that individual differences in reading performance are related to amount of activation in the pMTG, IFG, and AG. Previous studies have shown that better behavioral performance correlates with greater activation in the temporoparietal region, whereas lower behavioral performance correlates with greater activation in the IFG in semantic tasks, including category judgment (Shaywitz et al., 2002), and semantic judgment (Blumenfeld et al., 2006; Chee et al., 2001). In addition, the strength of structural connectivity of temporal-parietal regions correlates with the reading performance (Beaulieu et al., 2005; Klingberg et al., 2000). To our knowledge, no imaging study has tested for a link between functional connectivity in temporo-parietal cortex with behavioral performance in the semantic task.

Previous studies showing developmental changes in semantic processing have relied on cross-sectional samples (Blumenfeld et al., 2006; Chou et al., 2009; Lee et al., 2011). The current study is the first in Chinese to examine developmental changes in the neural correlates of semantic processing by using a longitudinal design. Longitudinal studies allow investigators to determine whether developmental changes are larger in certain age groups, and it allows investigators to predict changes over time (Gabrieli et al., 2015; Hoeft et al., 2007). In this study, we select two age cohorts because cross-sectional fMRI studies during semantic judgments in Chinese have shown that adolescents aged 12–15 might have better ability in selecting and retrieving semantic representations than children aged 8–11 (Lee et al., 2011; Lee et al., 2015). Several behavioral studies have also proposed the importance of forming and organizing links for semantic representations from childhood into early adolescence (Chan and Poon, 1999; Kavé, 2006; Matute et al., 2004; SauYeon et al., 2004). By examining the functional recruitment and connectivity in children (aged 8–11) and adolescents (aged 12–15) longitudinally, we aimed to determine whether there would be greater transition during semantic processing from childhood to early adolescence, as compared to the transition from early adolescence to late adolescence. In the present study, we also aimed to examine whether the initial brain activity and/or connectivity would be predictive of the future behavioral improvements. We expected that the initial brain activity in the pMTG and/or the initial connectivity of the pMTG with other regions may be predictive of the behavioral improvements for the transition from childhood to early adolescence, as compared for the transition from early adolescence to late adolescence.

2. Methods

2.1. Participants

In the semantic judgment task, a group of 30 native monolingual Chinese children (mean age = 11.8, standard deviation = 1.94, 14 girls) participated. To examine the developmental changes of conceptual knowledge (Lee et al., 2015), we divided participants into two age groups: children (8- to 11-year-old, $n = 15$, 8 girls) and adolescents (12- to 15-year-old, $n = 15$, 6 girls). The children participated in the experiment twice, with a two-year interval between scans. All 30 children were recruited from the Taipei city metropolitan area. The parents were given an informal interview to ensure that their children met the following inclusionary criteria: (1) right-handedness, (2) normal hearing (3) normal or corrected-to-normal vision, (4) free of neurological disease or psychiatric disorders, (5) no history of intelligence, reading, or oral-language deficits, and (6) no learning disability or attention deficit hyperactivity disorder (ADHD). After the administration of the informal interview, informed consent was obtained. The informed consent procedures were approved by the Institutional Review Board at the National Taiwan University Hospital. Standardized intelligence testing was administered, using the Wechsler Intelligence Scale for Children (WISC-III) Chinese version (The Psychological Corporation, 1999). The cutoff used for the WISC-III full IQ (FIQ) scores of participants was 84. Participants' standard scores (mean $\pm$ SD) were 110 ± 9 on the verbal scale and 107 ± 9 on the performance scale.

2.2. Functional activation task

The participants were given two practice sessions, one outside the scanner and the other in the scanner, to make sure that they understood the task. The practice items were different stimuli from those used in fMRI sessions. All participants achieved 80% for both practice sessions. The semantic judgment task included 48 related pairs and 24 unrelated pairs. Forty-eight character pairs were semantically related according to their free association values (mean = 0.14, SD = 0.13, ranging from 0.73 to 0.01) (Hue et al., 2005). The character pairs chosen from the Chinese association norm were based on their semantic relations including synonyms, antonyms, in the same category, or with similar functions (Lee et al., 2009). Character pairs were arranged in a continuous variable according to association values (Chou et al., 2009). These character pairs included both closely related pairs (e.g., 線 [thread]- 針 [needle]) with stronger association values and distantly related pairs (e.g., 季 [season]- 年 [year]) with weaker association values. In addition, twenty-four character pairs were semantically unrelated with zero association values (e.g., 斑 [spot]- 改 [change]). The participants were instructed to quickly and accurately press with their right hand the yes button to the related pairs and the no button to the unrelated pairs.

In the semantic judgment task, two visual Chinese characters were presented sequentially and the participants had to determine whether the two presented characters were related in meaning. Trials lasted 4500 ms and consisted of a solid square (500 ms), followed by the first character (800 ms), a 200 ms blank interval, and the second character (3000 ms). The participants were instructed to make a response during the presentation of the second character. The perceptual control condition had 24 pairs of non-characters. Non-characters were created by replacing radicals of real characters with other radicals that did not form real Chinese characters. Non-characters were larger (50 font size) than real characters (40 font size) in order to encourage participants to perform the task based on the recognition of low-level visual similarity and not on the extraction of semantic information. For the perceptual control condition, trials consisted of a solid square (500 ms), followed by the first non-character (800 ms), a 200 ms blank interval, and the second non-character for 3000 ms. Participants determined whether the pair of stimuli were identical or not by pressing a yes or no button with their right hand. There were also 24 baseline events as “null” trials so that we could better deconvolve the response to the lexical and perceptual trials. The participant was instructed to press a button when a solid square (1300 ms) at the center of the visual field turned to a hollow square (3000 ms) after a blank interval (200 ms). We chose to present data comparing the semantic to the perceptual control conditions to subtract out activation in the primary visual cortex that it is not likely due to semantic processing.

2.3. Stimulus characteristics

Several lexical variables were controlled across the related and unrelated conditions. First, all characters were monosyllabic. Second, the first and second character did not share radicals (i.e. the orthographic units of a character that provide clues to pronunciation and meanings of the character). Third, the first and second character together did not form a word (Sinica Corpus, 1998; Wu and Liu, 1987). In addition, in order to make sure that character pairs were controlled on lexical characteristics across related and unrelated conditions, we calculated 2 character (first, second) by 2 relatedness (related, unrelated)

ANOVAs. First, characters were matched for visual complexity (in terms of strokes per character) across conditions. A 2 character (first, second) $\times$ 2 condition (related, unrelated) ANOVA showed that the main effect of relatedness nor its interaction with character was significant. Second, characters were matched for written frequency for adults (Wu and Liu, 1987) and written familiarity for children across the related and unrelated conditions. Familiarity scores were obtained from pre-tests in which all the characters were rated on a 7-point scale by thirty age matched children who were native Mandarin speakers from Taiwan. A 2 character (first, second) $\times$ 2 condition (related, unrelated) ANOVA showed no main effects or interactions with the frequency or the familiarity measure. The correlation of the character frequency or familiarity measure with association strength was not significant indicating that association effects should not be due to frequency or familiarity differences.

2.4. MRI data acquisition

Participants lay in the scanner with their head position secured with a specially designed vacuum pillow. An optical response box was placed in the participants' right hand. The head coil (8-channel head coil) was positioned over the participants' head. Participants viewed visual stimuli projected onto a screen via a mirror attached to the inside of the head coil. Each participant performed two functional runs (4.7 min each). All images were acquired using a 3 Tesla Siemens Trio scanner (Siemens, Erlangen, Germany). Gradient-echo localizer images were acquired to determine the placement of the functional slices. For the functional imaging studies, a susceptibility weighted single-shot EPI (echo planar imaging) method with BOLD (blood oxygenation level-dependent) was used. Functional images were collected parallel to the AC-PC plane with interleaved whole brain EPI acquisition from bottom to top. The following scan parameters were used: TE = 24 ms, flip angle = 90, matrix size = 64×64 , field of view = 25.6 cm, slice thickness = 3 mm, number of slices = 34, TR = 2000 ms. Each functional run had 136 image volumes. In addition, a high resolution, T1 weighted 3D image was acquired (TR = 1560 ms, TE = 3.68 ms, flip angle = 15, matrix size = 256×256 , field of view = 25.6 cm, slice thickness = 1 mm, number of slices = 192). The orientation of the 3D image was identical to the functional slices. The task was administered in a pseudorandom order for all subjects, in which the order of related, unrelated, perceptual, and baseline trials was optimized for event related design (Burock et al., 1998). We used the Optseq script for randomized event-related design (<http://surfer.nmr.mgh.harvard.edu/optseq>, written by D. Greve, Charlestown, MA) that implemented Burock et al. (1998)'s approach.

2.5. fMRI Image analysis

Data analysis was performed using SPM8 (Statistical Parametric Mapping). The functional images were corrected for differences in slice-acquisition time to the middle volume and were realigned to the first volume in the scanning session using affine transformations. No participant had more than 3 mm of movement in any plane. Co-registered images were normalized to the MNI (Montreal Neurological Institute) average template (12 linear affine parameters for brain size and position, 8 non-linear iterations and $2 \times 2 \times 2$ nonlinear basis functions). Statistical analyses were calculated on the smoothed data (6 mm isotropic Gaussian kernel), with a high pass filter (128 s cutoff period) in order to remove low frequency artifacts.

2.5.1. Whole-brain Analysis—Data from each participant was entered into a general linear model using an event-related analysis procedure (Josephs and Henson, 1999). Character pairs were treated as individual events for analysis and modeled using a canonical HRF (Hemodynamic Response Function). There were four event types: related, unrelated, perceptual, and baseline. For the related pairs, association strength was an item-level parametric modulator in order to differentiate semantic relatedness as a continuous variable according to log transformed free association strength (Hue et al., 2005). The analysis of association strength was based on the related pairs and was not in comparison to baseline (also see Chou et al., 2009). The resulting model coefficients from contrasts of the canonical HRF in single subject models were entered into subsequent second-order random effects analyses in a whole brain analysis.

In the first series of analyses, to examine the common neural processes for semantic processing in the two age groups across two time points, we conducted a whole-brain conjunction analysis, using a full factorial design (between subject factor: age group, within subject factor: time point) on the contrast of [related vs. perceptual control] (Meyer et al., 2015; Nichols et al., 2005; Price and Friston, 1997). In the second series of analyses, we examined the effect of the continuous variable of log transformed association strength for the related pairs (Hue et al., 2005). We employed a 2 age group (children, adolescents) by 2 time point (time1, time2) factorial design. To further investigate the interaction effect, we conducted following comparisons for the strong association and weak association separately: (1) [adolescents (time 2 - time 1)] > [children (time 2 - time 1)], (2) [children (time 2 - time 1)] > [adolescents (time 2 - time 1)], (3) adolescents (time 2 - time 1) and (4) children (time 2 - time 1). Conjunction analysis and factorial design analyses are $p < .05$ FDR (false-discovery error rate) corrected with clusters greater than or equal to 10 voxels. The association effects were calculated within an inclusive mask ($p < 0.005$ uncorrected) from the conjunction analysis. Finally, we extracted the beta values from peak voxels of brain regions that showed association effects for the regression analyses (see below).

2.5.2. Psychophysiological Interaction Analysis—Functional connectivity analysis was carried out using Psychophysiological Interaction (PPI) analyses as implemented in SPM 8. In general, PPI tests the condition-specific connectivity without assuming a direction of influence (Friston et al., 1997). In the present study, we selected the seed region guided both by previous studies (Chou et al., 2009; Lee et al., 2011; Wu et al., 2012) and based on the results of our whole brain analyses for the interaction effect for activation (see Table 2). Then, the PPI analysis estimates functional connectivity between the signal of the time series of the seed voxels and those of all other voxels in the whole brain. In addition, reported areas of connectivity are $p < .05$ FDR (false-discovery error rate) at the peak level. Specifically, PPI explains variation in brain activity by the interplay of two factors: (a) the input of a selected seed region (the physiological variable, Y regressor) and (b) a cognitive process as defined by a contrast (the psychological variable, P regressor). PPI analyses create an interaction factor consisting of the product of a vector representing the time series of brain activation in the region of interest (i.e. the physiological variable) and a vector representing the condition contrast (i.e. the psychological variable) (Gitelman et al., 2003).

Based on the results of our whole brain analyses for the interaction effect, posterior middle temporal gyrus (pMTG, BA 21) was selected as the seed region. In addition, in order to examine the condition-specific connectivity, the 48 related pairs in the semantic judgment task were further divided into 24 strong and 24 weak association pairs according to their association values. We measured functional connectivity by examining covariation for contrasts “strong vs. perceptual controls” and “weak vs. perceptual controls” across the whole brain with the activation within the pMTG. The size of a seed region was defined as a sphere with a radius of 6 mm. To perform the PPI analyses, the deconvolved timeseries for the seed regions were extracted from the normalized data for each participant. The physiological variable (Y regressor), the psychological variable (P regressor), and their interaction (PPI regressor) were calculated in the GLM model as regressors for each participant. The estimates for PPI were then entered into second-order random-effect analysis using a 2 age group (children, adolescents) by 2 time point (time1, time2) factorial design to examine the differences between age groups. To further investigate the interaction effect, we conducted following comparisons for strong vs. perceptual controls and weak vs. perceptual controls separately: (1) [adolescents (time 2 - time 1)] > [children (time 2 - time 1)], (2) [children (time 2 - time 1)] > [adolescents (time 2 - time 1)], (3) adolescents (time 2 - time 1) and (4) children (time 2 - time 1). Reported areas of connectivity for the interaction effects (i.e. IPL) are $p < .05$ FDR (false-discovery error rate) corrected with a sphere of 10 mm radius from the meta-analyses (Wu et al., 2012). Finally, the estimates of PPI values were extracted from each participant for further regression analyses (see below).

2.5.3. Correlation Analysis—T2-T1 Beta values and T2-T1 PPI values were correlated with T2-T1 behavioral improvement (i.e. accuracy and reaction times, separately) for the strong association and weak association separately.

2.5.4. Regression Analyses—The relationship between brain activation, connectivity, and behavioral improvement (i.e. accuracy, reaction times) from Time 1 to Time 2 was examined using a hierarchical stepwise regression model in SPSS. Beta values, PPI values, and behavioral performance at Time1 for each participant were used as regressors of interest, along with behavioral improvement as the dependent variable, in order to determine whether regional activity or connectivity between regions was predictive of behavioral improvement during semantic judgments.

Results

3.1. Behavior performance

3.1.1. Analyses of accuracy within and between age groups—In the child group, accuracy (mean $\pm$ SD) for the strong and weak association in time 1 was $81 \pm 4\%$ and $76 \pm 9\%$, respectively. In addition, accuracy (mean $\pm$ SD) for the strong and weak association in time 2 was $90 \pm 9\%$ and $87 \pm 8\%$, respectively. In the adolescent group, accuracy (mean $\pm$ SD) for the strong and weak association in time 1 was $91 \pm 8\%$ and $82 \pm 5\%$, respectively. In addition, accuracy (mean $\pm$ SD) for the strong and weak association in time 2 was $93 \pm 7\%$ and $86 \pm 9\%$, respectively. A 2 age $\times$ 2 time point $\times$ 2 association repeated measures ANOVA revealed a main effect of age [$F(1, 28) = 7.98, p < .001$], a main effect of time point

[$F(1, 28) = 32.82, p < .001$], a main effect of association [$F(1, 28) = 15.16, p < .001$], and an interaction between age and time point [$F(1, 28) = 8.11, p < .001$]. A simple main effect analysis to evaluate the interaction for the two age groups was further conducted separately. The simple main effects analysis showed an improvement from time 1 to time 2 for children, $F(1, 28) = 36.79, p < .001$, but only a trend for improvement from time 1 to time 2 for adolescents, $F(1, 28) = 4.15, p = .051$. There were no other significant effects.

3.1.2. Analyses of reaction times within and between age groups—In the child group, reaction times (mean $\pm$ SD) for the strong and weak association in time 1 were 1153 ± 232 ms and 1202 ± 257 ms, respectively. In addition, reaction times (mean $\pm$ SD) for the strong and weak association in time 2 were 941 ± 183 ms and 1015 ± 154 ms, respectively. In the adolescent group, reaction times (mean $\pm$ SD) for the strong and weak association in time 1 were 1022 ± 228 ms and 1105 ± 213 ms, respectively. In addition, reaction times (mean $\pm$ SD) for the strong and weak association in time 2 were 837 ± 182 ms and 903 ± 195 ms, respectively. A $2 \text{ age} \times 2 \text{ time point} \times 2 \text{ association}$ repeated measures ANOVA revealed a main effect of time point [$F(1, 28) = 25.27, p < .001$], and a main effect of association [$F(1, 28) = 40.14, p < .001$]. There were no other significant effects.

3.2. Brain activation patterns

3.2.1. Conjunction activation for 2 age groups across time points—The conjunction analysis showed common activations that have been implicated in previous studies of semantic processing, namely in left inferior frontal gyrus, middle temporal gyrus, and inferior parietal lobule. All activation differences are reported in the tables. Table 2 shows conjunction activation for the related pairs versus the perceptual control pairs for both age groups in time 1 and time 2. The related pairs compared to the perceptual controls produced greater activation in the ventral regions of left inferior frontal gyrus (BA 45, 47), pMTG (BA 21) and IPL (BA 40).

3.2.2. Interaction effects between age and time point—Table 3 lists the main effects and interaction effects for both associations. First, the interaction within the strong association was not significant. For strong association, we pooled the brain activation across two time points. In addition, we pooled the brain activation across two age groups to observe common activations for time 1 and time 2. All activation differences are reported in the tables. Second, the interaction within the weak association was significant. Greater activation in the pMTG with time 2 versus time 1 was larger for the children as compared to that for the adolescents (Figure 1a). In addition, a series of analyses of time within each age group was performed separately. Greater activation in the pMTG with time 2 versus time 1 in the weak association was significant for the children (Figure 1b), but not for the adolescents. Third, because common activations were found in the IFG for the weak association at time 1 and time 2, we pooled the brain activation across two time points. The weak association elicited greater activation in the IFG for both age groups. In addition, we pooled the brain activation across two age groups to observe the common activations for time 1 and time 2. The weak association elicited greater activation in the IFG for both time points.

3.2.3. Functional connectivity: interaction of age by time—Table 4 lists the PPI results. First, the interaction within the contrast of the strong vs. perceptual controls was not significant. Second, the interaction within the contrast of the weak vs. perceptual controls was significant. The functional connectivity between the pMTG (BA 21) and left IPL (BA 40) was larger with time 2 versus time 1 for the children as compared to that for the adolescents (Figure 1c). In addition, a series of analyses of time within each age group was performed separately. The functional connectivity between the pMTG (BA 21) and left IPL (BA 40) was significant with time 2 versus time 1 in the weak association for the children, but not for the adolescents (Figure 1d).

3.2.4. Correlation Analysis—For strong association pairs, T2-T1 on brain activity and functional connectivity was not significant. Thus, we did not perform the correlation for strong association. For the weak association, correlations were used to determine whether brain activity in the pMTG or connectivity between the pMTG and IPL was related to T2-T1 behavioral improvement (i.e. accuracy and reaction times, separately) for the weak association. First, correlation between T2-T1 beta values and T2-T1 improvement in accuracy showed a trend [$r = 0.34$, $p = 0.07$]. Second, correlation between T2-T1 PPI values and T2-T1 improvement in accuracy was significant [$r = 0.38$, $p = .037$]. There were no significant effects for reaction times. It has been proposed that accuracy is a sensitive measurement index for semantic processing for children but not for adults, because adults' accuracy levels are close to the ceiling level (Hashimoto et al., 2007). In support of this, previous studies found accuracy, not reaction times, to be sensitive to age-related changes in semantic processing for children (Lee et al., 2014; Hung et al., 2010; Wong et al., 2011).

3.2.5. Regression Analysis—A hierarchical stepwise regression model was used to determine whether brain activity in the pMTG or connectivity between the pMTG and IPL was predictive of T2-T1 behavioral improvement (i.e. accuracy, reaction times) for each age group. We performed a hierarchical stepwise regression analysis, using the T2-T1 improvement in accuracy for the weak association as the dependent variable. In the first step, Time 1 accuracy for the weak association and Time 1 pMTG beta values were all entered as predictors. In the second step, Time 1 PPI value between the pMTG and IPL was entered as the predictor. The results showed that the regression analysis was not significant for the adolescents. In contrast, for the children, a regression model including Time 1 accuracy, pMTG beta values, and PPI value was significant (Model $F(3, 11) = 9.92$, $p < .05$). Moreover, inclusion of Time 1 PPI value in the second step additionally improved the model (R^2 Change = .118, Change $F(1, 11) = 4.87$, $p < .05$), indicating that this functional connectivity accounted for a significant portion of unique variance even after partially for Time 1 accuracy and pMTG beta values. Alternatively, we performed another hierarchical stepwise regression analysis for the weak association, using Time 1 accuracy and Time 1 PPI in the first step and Time 1 pMTG beta values in the second step. The results showed that the analysis was not significant for the adolescents. In contrast, for the children, the model including Time 1 PPI value in the first step was significant (Model $F(2, 11) = 12.78$, $p < .05$), but Time 1 pMTG beta values in the second step did not additionally improve the model (R^2 Change = .053, Change $F(1, 11) = 2.21$, $p > .05$). However, no significant results were found for regression analysis using reaction times as the dependent variable. In short, we

considered accuracy as a more sensitive index for children. Taken together, the regression analyses showed that Time 1 PPI value significantly predicted T2-T1 behavioral improvement in accuracy for the children.

3. Discussion

The goal of this study was to determine the initial-to-outcome relationship of brain activation and functional connectivity to behavioral performance in semantic processing. To our knowledge, no research has directly examined this relationship longitudinally in Chinese children. The results demonstrated that processing weaker association pairs elicited greater activation in the pMTG (BA 21), reflecting greater developmental increase between time 1 and time 2 for the children (aged 8–11) as compared to that for the adolescents (aged 12–15). In addition, the change from time 1 and time 2 in connectivity between the pMTG and IPL (BA 40) was greater for the children as compared to the adolescents for weak association pairs. Furthermore, the connectivity between these two regions was uniquely predictive of the behavioral improvement for the children, over and above variance explained by amount of activation.

Our first major finding was that processing weak association pairs produced greater activation in the pMTG, reflecting greater developmental increases from time 1 to time 2 for the children as compared to that for the adolescents. Several cross-sectional studies have identified age-related changes in the pMTG for meaning processing in Chinese (Chou et al., 2009; Lee et al., 2011). This region is often being considered as the storage of lexical representations (Binder et al., 2009; Blumenfeld et al., 2006; Lau et al., 2008). The weak association pairs may require extensive access to lexical representations to identify overlapping features for distant relationships. In support of this, many studies have found that the posterior middle temporal gyrus is involved in various comprehension tasks that require high semantic control demands (Assaf et al., 2006; Badre et al., 2005; Boulenger et al., 2009; Mashal et al., 2009; Noppeney et al., 2004; Rodd et al., 2005; Snyder et al., 2007; Thompson-Schill et al., 1997; Wagner et al., 2001; Zempleni et al., 2007). Moreover, transcranial magnetic stimulation (TMS) to the posterior middle temporal gyrus elicited a disruption to task performance requiring high compared to low semantic control demands, showing deficits to access distant associations (Whitney et al., 2010).

It has been proposed that the pMTG plays an active role in comprehension tasks that essentially bridge semantic representations and semantic control (Noonan et al., 2013). The pMTG may be related to a flexible mechanism of processing concepts, reflecting a selective control over certain aspects of meaning that is appropriate to the task or context. Behavioral studies have revealed an early reliance on forming and organizing semantic relations that continues into late childhood/early adolescence (Chan and Poon, 1999; Kavé, 2006; Koren et al., 2005; Matute et al., 2004; SauYeon et al., 2004). In order to examine the maturational changes of this early reliance on forming relations, participants were stratified into the children and adolescents. Several studies propose that structural and functional changes during this transition period might be a benefit by providing cognitive flexibility for learning to bind, store, and retrieve lexical representations (Ramscar and Gitcho, 2007; Rosselli et al., 2014; Thompson-Schill et al., 2009). We extend these previous theoretical formulations by

identifying more prominent longitudinal changes in the pMTG for the children compared to the adolescents. Children may have learned how to process semantic knowledge in a more flexible way, involving greater improvements to access lexical representations with distant relationships.

Our second major finding revealed longitudinal changes for the children in functional connectivity between the pMTG and IPL for weak association pairs. The IPL has been implicated as the phonological store for working memory that is thought to offer temporary maintenance for verbal information (Buchsbaum and D'E-sposito, 2008; Chen & Desmond, 2005; Ravizza et al., 2004). Behavioral studies point to direct links between phonological working memory, word learning and semantic development (Baddeley et al., 1998; Gathercole et al., 1992; Vulchanova et al., 2014). Baddeley's learning model (1998) proposes that the learning system detects the repeated features of temporary representations in the phonological store in order to support the construction of long-term lexical representations. The detection of repeated features may be especially important for weakly related pairs because of the few overlapping semantic features for these pairs. This paucity of overlap is a challenge for the learning system as it must relate new input to existing long-term representations in order to establish the semantic relationship. In support of Baddeley's learning model, a behavioral study in Chinese demonstrated positive correlations between working memory and semantic skills during childhood (grade 1 to grade 4) (So & Siegel, 1997). Their results support the role of working memory in semantic processing, by helping the child to recall or process the meaning and sounds of words. Overall, the current findings of a functional connectivity between the pMTG and IPL for the children are in line with previous behavioral studies, reflecting that an early development of semantic representations is facilitated by enhanced engagement of phonological short-term memory (Baddeley et al., 2003).

Our third major finding was that connectivity between the pMTG and IPL at time 1 in weak association pairs was uniquely predictive of behavioral improvement from time 1 to time 2 for children, but not for adolescents. Although previous work has noted a relationship between behavioral lexico-semantic knowledge with either MTG activity or IPL activity, to our knowledge, no research has directly linked behavioral improvement to functional connectivity at an earlier time point. Our results demonstrate the unique variance of temporo-parietal connectivity over and above activation and behavior at time 1. A magnetoencephalography (MEG) study examined the brain activation profiles of adolescents with reading difficulties (RD). Based on their performance in a reading fluency test one year later, RD students who showed positive response to intervention were classified as adequate responders (AR). They found that left temporoparietal (IPL and pMTG) activation in the first year was a significant predictor for gains in reading fluency for the AR group in the second year (Rezaie et al., 2011). These results demonstrate that these regions may serve as key components of the brain circuit for response to intervention in struggling readers. In the current study, we extend previous research by directly linking connectivity between these two regions to longitudinal behavioral improvements in typically developing children. It is known that the phonological store plays an important role in learning novel words, by establishing relations to existing long-term representations (Baddeley et al., 1998). Evidence from developmental studies has found that good phonological memory facilitates fast and

efficient learning of novel/unfamiliar lexical items in early childhood (Gathercole et al., 1992; Vulchanova et al., 2014). The functional connectivity between pMTG with IPL in our study suggests that early development of semantic representations is supported by the use of phonological working memory.

The current findings of greater activation in pMTG from time 1 to time 2 for the children as compared to that for the adolescents are congruent with the notion of reliance on forming and organizing links for semantic representations in early childhood/early adolescence (aged 8–11) (SauĶeon et al., 2004). However, our results did not support the notion of later reliance on strategic retrieval in late adolescence/early adulthood (aged 12–15). We did not find evidence for greater reliance on the IFG for adolescents as compared to children, but we find that the weak association elicited similar activation in IFG for both age groups across two time points. The lack of consistency with prior studies might be due to the differences in task difficulty. The abovementioned study (SauĶeon et al., 2004) used the verbal fluency task that engages both switching (i.e. search and retrieval of different semantic subcategories) and clustering processes (i.e. search and retrieval of exemplars from the same subcategory). Thus, the verbal fluency task might be more sensitive to effortful semantic processing, reflecting greater reliance on strategic retrieval for adolescents compared to children. In the present study, the semantic judgment task might be less difficult than the verbal fluency task due to the possibility that our stimuli were mainly based on the same semantic categories (Wong et al., 2014). Thus, we found comparable retrieval difficulty for both age groups.

The findings and interpretations of this study should be considered in light of its limitations. First, due to the small sample size in the present study, statistical power was limited when the groups were split by age. Second, unequal numbers of boys and girls in the two age groups might also bias our interpretations. Future studies with a larger sample size and an equal number of boys and girls are required to examine semantic processing longitudinally. Third, in the present study, we relied on parents' reports and IQ performance to ensure that participants did not have a history of intelligence, reading, attention, or oral-language deficits. However, we did not verify the existence of ADHD or reading abilities using other objective standardized measures and therefore we cannot exclude the possibility that our findings may be affected by these factors. Another limitation of the study is the lack of objective measures of phonological working memory which limits our interpretation of the relationship between working memory and semantic processing.

In conclusion, we showed that greater developmental increase for children as compared to adolescents in the left pMTG for weaker association pairs, suggesting relatively early changes before adolescence in the semantic processing network. However, the most important finding is a uniquely predictive relationship between the initial pMTG-IPL connectivity and future behavioral improvement for weaker association pairs. Thus, our results highlight the importance of temporo-parietal connectivity as a significant predictor for conceptual efficiency longitudinally. The IPL has been implicated as a core region involved in phonological short term memory, and therefore may be a language learning device that allows for the acquisition and refinement of semantic representations in pMTG.

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Highlights

- We explored if initial brain measures could predict future behavioral improvement.
- Child participants took part a longitudinal fMRI study in a semantic judgment task.
- Greater age-related increase in the left pMTG for children relative to adolescents.
- Initial pMTG-IPL connectivity predicted future accuracy improvement for children.
- Phonological working memory relates to the acquisition of semantic representations.

Figure 1.

Developmental changes in the weaker association in the visual semantic task. (a) Greater developmental increases (from time 1 to time 2) were observed in left posterior middle temporal gyrus (pMTG, BA 21) for the younger children as compared to the older children (b) Greater activation in the posterior middle temporal gyrus (BA 21) from time 1 to time 2 was significant only for the children. (c) The functional connectivity between MTG (BA 21) and left inferior parietal lobule (IPL, BA 40) from time 1 to time 2 was larger for the children as compared to that for the adolescents for the contrast of weak vs. perceptual controls (d) The functional connectivity between MTG (BA 21) and left IPL (BA 40) from time 1 to time 2 was significant only for the children

Table 1

Means (SDs) for subject characteristics for children and adolescents in the experiment

	Children (n =15)	Adolescents (n = 15)
Age at Time 1 (years)	10.1 (0.9)	13.5 (0.8)
Age at Time 2 (years)	12.0 (0.6)	15.5 (0.9)
Follow-up intervals (months)	26.1 (0.7)	25.8 (0.4)

Table 2

Conjunction activation for two age groups across two time points.

Contrasts	Regions	H	BA	z-test	voxels	x	y	z
Related-perceptual	Inferior frontal gyrus	L	47	6.77	1235	-48	26	-2
	Inferior frontal gyrus	L	45	-	-	-48	23	10
	Middle temporal gyrus	L	21	4.58	151	-57	-43	4
	Inferior parietal lobule	L	40	-	-	-57	-47	25
	Insula	R	13		129	30	23	1
	Caudate	L	-	4.65	478	-15	-4	13

Note. H: hemisphere, L: left, R: right, BA: Brodmann's Area. Coordinates of activation peak(s) within a region based on a z-test are given in the MNI stereotactic space (x, y, z). Regions surviving $p < .05$ FDR (false-discovery error rate) corrected are presented.

Table 3

Activation for association effects

Condition	Regions	H	BA	z-test	voxels	x	y	z
Across time points								
Strong	Children	Superior frontal gyrus	L 8	4.06	20	-12	29	55
		Medial frontal gyrus	L 8	3.67	13	-6	41	46
		Caudate	L -	3.41	13	-12	-7	19
	Adolescents	Middle temporal gyrus	L 21	3.82	19	-54	-54	4
		Caudate	L -	3.75	20	-12	11	10
		Superior frontal gyrus	L 8	3.73	198	-9	26	58
Across age groups								
Strong	Time1	Middle temporal gyrus	L 21	4.13	48	-54	-37	-5
		Medial frontal gyrus	L 8	3.83	87	-6	44	46
		Angular gyrus	L 39	3.41	13	-51	-51	22
		Cingulate	L 24	3.38	11	-3	-7	28
	Time2	Superior frontal gyrus	L 8	4.32	68	-9	29	55
		Caudate	R -	4.11	28	12	17	10
Across time points								
Weak	Children	Inferior frontal gyrus	L 45	3.69	243	-45	26	21
		Medial frontal gyrus	R 6	3.15	29	0	14	49
	Adolescents	Insula	R 13	3.48	67	33	20	4
		Inferior frontal gyrus	L 45	3.43	100	-40	23	13
		Middle frontal gyrus	L 9	3.23	132	-48	17	37
		Cingulate gyrus	R 32	3.21	56	3	17	46
Across age groups								
Weak	Time 1	Medial frontal gyrus	R 8	3.88	70	3	23	43
		Inferior frontal gyrus	L 45	3.62	115	-42	17	21
	Time 2	Inferior frontal gyrus	L 45	3.83	10	-42	26	13
		Precentral gyrus	L 9	3.83	13	-54	5	40
	Interaction: [children (T2-T1)>adolescents (T2-T1)]							

Condition	Regions	H	BA	z-test	voxels	x	y	z
Weak	Middle temporal gyrus	L	21	4.41	178	-54	-49	4
		Effect of time in the children (T2-T1)						
Weak	Middle temporal gyrus	L	21	3.43	22	-57	-43	1

Note. See Table 2 note. Voxels: number of voxels in cluster at $p < .05$ FDR (false-discovery error rate) corrected are presented. The activation maps from the conjunction analysis were used as inclusive masks ($p < 0.005$ uncorrected) for the association analyses in this study.

Table 4
Psychophysiological Interaction effects for the contrast of the weak versus perceptual controls

Regions	H	BA	z-test	voxels	X	Y	Z
<i>Interaction: [children (T2-T1)>adolescents (T2-T1)]</i>							
Inferior parietal lobule	L	40	3.08	105	-54	-31	37
<i>Effect of time in the children (T2-T1)</i>							
Inferior parietal lobule	L	40	2.66	28	-57	-31	37

Note. See Table 2 note. Reported areas of connectivity for the interaction effects (i.e. IPL) are $p < .05$ FDR (false-discovery error rate) corrected with a sphere of 10 mm radius from the meta-analyses (Wu et al., 2012).