Tuning of the Visual Word Processing System: Distinct Developmental ERP and fMRI Effects

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Abstract: Visual tuning for words vs. symbol strings yields complementary increases of fast occipito-temporal activity (N1 or N170) in the event-related potential (ERP), and posterior–anterior gradients of increasing word-specific activity with functional magnetic resonance imaging (fMRI) in the visual word form system (VWFS). However, correlation of these coarse ERP and fMRI tuning responses seems limited to the most anterior part of the VWFS in adult and adolescent readers (Brem et al. [2006]: *Neuroimage* 29:822–837). We thus focused on fMRI tuning gradients of young readers with their more pronounced ERP print tuning, and compared developmental aspects of ERP and fMRI response tuning in the VWFS. Children (10.3 y, $n = 19$), adolescents (16.2 y, $n = 13$) and adults (25.2 y, $n = 18$) were tested with the same implicit reading paradigm using counterbalanced ERP and fMRI imaging. The word-specific occipito-temporal N1 specialization, its corresponding source activity, as well as the integrated source activity (0–700 ms) were most prominent in children and showed a marked decrease with age. The posterior–anterior fMRI gradient of word-specific activity instead which was fully established in children did not develop further, but exhibited a dependence on reading skills independent of age. To conclude, prominent developmental dissociation of the ERP and fMRI tuning patterns emerged despite convergent VWFS localization. The ERP response may selectively reflect fast visual aspects of print specialization, which become less important with age, while the fMRI response seems dominated by integrated task- and reading-related activations in the same regions. *Hum Brain Mapp* 30:1833–1844, 2009. © 2009 Wiley-Liss, Inc.

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INTRODUCTION

Reading has long been known to involve collaboration of visual areas specialized for print processing with higher order language areas in the brain [Cohen et al., 2003; Déjerine, 1892]. Due to the importance of visual processes for reading, a major focus in recent research has been on the role of visual processing areas in normal and impaired readers as well as in young “beginning” and adult “proficient” readers. Along with lesion studies, metabolic brain imaging techniques such as positron emission tomography (PET) [Petersen et al., 1990; Price et al., 1996] or functional magnetic resonance imaging (fMRI) [Cohen et al., 2002,

2003; Turkeltaub et al., 2003] shed light onto functional properties of areas engaged in visual word processing. Considerable visual and orthographic word processing is accomplished in ventral occipito-temporal cortex areas [Booth et al., 2001; Brown et al., 2004; Cohen et al., 2003; Dehaene et al., 2002; Pugh et al., 1996; Schlaggar et al., 2002; Tagamets et al., 2000], referred to as the visual word form system (VWFS) [Vinckier et al., 2007], with the VWF area (VWFA) in the left midfusiform gyrus in its center [Cohen and Dehaene, 2004; Cohen et al., 2000]. The term VWFS emphasizes its consistent activation in tasks requiring explicit [Cohen et al., 2002] and implicit visual word processing [Price et al., 1996; Tagamets et al., 2000]. The word-specificity of this area has been disputed because non-orthographic strings of false fonts, symbols or letters, and even objects can activate the VWFA to a similar degree [Brem et al., 2006; Moore and Price, 1999; Price et al., 1996; Tagamets et al., 2000; Turkeltaub et al., 2003]. However, (i) the proximity of multimodal areas and blurring of differential responses due to insufficient spatial resolution or intersubject variability [Cohen and Dehaene, 2004], (ii) insufficient temporal resolution [Dale et al., 2000; Furey et al., 2006], or (iii) top-down effects of increased processing demands for control stimuli as in repetition detection tasks [Brem et al., 2006; Tagamets et al., 2000] may all obscure word-specificity in the VWFS [Vinckier et al., 2007]. The more consistent finding is that the mature VWFS exhibits a posterior–anterior gradient of word or print specificity [Brem et al., 2006; James et al., 2005; Vinckier et al., 2007], with differential word - symbol string activation increasing when moving towards more anterior portions of the VWFS.

Event-related potential (ERP) and magnetencephalographic (MEG) results parallel fMRI findings of print activation in the VWFS, but additionally highlight that its time-course follows primary visual processing and marks the initial (<250 ms) phase of specialized print processing [Dale et al., 2000; Helenius et al., 1999; Marinkovic et al., 2003; Nobre et al., 1994; Parviainen et al., 2006; Tarkiainen et al., 1999] for both averaged and oscillatory activity [Pammer et al., 2004]. Intracranial inferior occipito-temporal recordings also reveal differential activation to visually presented words, faces and other visual stimuli peaking at 140–220 ms [Allison et al., 1994; Mainy et al., 2008; Nobre et al., 1994]. The corresponding scalp ERP is the N1 (N170, VPP) with occipito-temporal negativity and sources [Brem et al., 2006; Maurer et al., 2005; Proverbio et al., 2008]. This N1 shows coarse word- or print-specificity. Its amplitudes are usually larger to word-like stimuli (words, letter, and pseudofont strings) than to nonsense character strings (made from symbols, icons, or other forms), particularly over the left hemisphere, but similar to categories of orthographic stimuli (words, pseudowords, and consonant strings) or print-like false fonts [Bentin et al., 1999; Eulitz et al., 2000; Maurer et al., 2005; Proverbio et al., 2008; Rossion et al., 2003; Schendan et al., 1998; Xue et al., 2008].

The typical N1 topography develops when children learn to read. Word-specific N1 activity is especially pronounced in beginning readers [Maurer et al., 2005, 2006]. In contrast to the distinct word-specific N1, no word-specific fMRI activity was found in the VWFS of children when comparing words and symbols [Turkeltaub et al., 2003], thereby questioning the correspondence of ERP and fMRI activity, when assuming that the hemodynamic response is mainly driven by the source of the N1. However, similar to the N1, developmental attenuations often characterize fMRI activation in lower level extrastriate cortex. These reductions were usually more pronounced in the right hemisphere [Brown et al., 2004; Church et al., 2008; Gaillard et al., 2000; Holland et al., 2001; Schapiro et al., 2004; Shaywitz et al., 2002; Turkeltaub et al., 2003] and have been associated with regressive changes [Brown et al., 2004] reflecting visual fine tuning in extrastriate areas or the emerging capacity for more efficient or specialized processing [Church et al., 2008].

The majority of developmental studies of the reading network continue to use either only electrophysiological or hemodynamic imaging techniques. However, these imaging techniques do not fully converge [Vitacco et al., 2002]. They are sensitive to different aspects of information processing such as transient or sustained responses [Furey et al., 2006], and thereby capture only certain aspects of temporal or spatial alterations in brain networks, while others remain undetected.

With our (sequential) multimodal approach, we aimed to track the development of word-specificity in the VWFS during implicit visual word processing, focusing on convergence and dissociation of ERP and fMRI findings in the same children, adolescents and adults.

MATERIALS AND METHODS

For full details regarding tasks and procedure in adults and adolescent see Brem et al. [2006]. The description below focuses on the new group (children) and the new analyses.

Participants

After excluding 5 children due to excessive head movement during fMRI scanning, 19 children (age 9.3–11.6 y, mean 10.3 y, school grades 4–5, 9 boys), 13 adolescents (age 15.2–17.3 y, mean 16.2 y, 5 males) and 18 adults (age 19.8–30.8 y, mean 25.2 y, 9 males) were included in statistical analyses. All were native Swiss-German speaking, right-handed, had normal or corrected vision and none had a neurological or psychiatric disease, or reading disorder (only subjects performing in the normal range (>10%) of the reading test were included in the analyses, for details see Supporting Information (SM) online). Children's IQ was estimated using the Block design subtest from the German HAWIK-III and only children with an estimated IQ ≥ 80 points (mean $\pm$ SD = 106.6 $\pm$ 11.3) could partici-

pate. For participation, adults and adolescents were paid (60CHF) and children received a present of similar value. Each adult subject and one parent/caretaker of the under aged adolescents and children gave informed consent to the study, which had been approved by the local ethics commission.

Procedure and Task

All subjects took part in separate counterbalanced EEG and fMRI sessions (average intersession interval 13 days). In both sessions, subjects had to perform the same visual word and symbol string processing task which required detecting 16.7% immediate repetitions of words and symbol strings presented on noise and no-noise background [Brem et al., 2006 and SM-methods] as illustrated in SM Figure 1. For all analyses, noise and no-noise background conditions were pooled.

Behavioral Analyses

The mean overall accuracy (including targets and false alarms) in the word and symbol string processing task was high (see Supporting Information Table I) in all three groups (children: 95.4%, adolescents: 97.6%, adults: 97.9%). The data from one boy were not included in the behavioral analyses, since his data were not logged during the EEG session, leaving the behavioral data of 18 children. Performance differences between the three age groups, and imaging methods were examined by computing separate MANOVAs for reaction time and target accuracy including the within subject factors condition (words, symbol strings) and method (EEG, fMRI) and between subject factor age group (children, adolescents, adults). The influence of task repetition was tested using a MANOVA with within subject factor condition and session (first vs. second session). In addition a correlation analysis of reading performance (reading speed in the local pseudoword reading test) and age was computed.

ERP Recording and Processing

Participants sat in a recording room watching a computer display for the 2.5 hour EEG session. ERPs were recorded from 63 channels at 500 Hz (0.1–70 Hz, calibrated technical zero baselines, Fz as recording reference, AFz as ground; see [Brem et al., 2006]. The impedance for >85%

Figure 1.

Waveforms of GFP (top), left (O1': middle) and right (O2': bottom) occipito-temporal electrodes to words (solid lines) and symbol strings (dotted lines) in children (red), adolescents (blue) and adults (black). Clearly visible are major decreases in amplitude (and latency) as well as the pronounced decrease in the difference between words and symbols with age.

TABLE I. MNI coordinates and anatomical brain regions for fMRI activation maxima of the contrast words–symbol strings

			MNI			<i>k</i>	<i>Z</i> (voxel)
	Region		<i>x</i>	<i>y</i>	<i>z</i>		
Children	L	Superior temporal gyrus	−60	−45	6	475	6.76
	L	Inferior frontal gyrus	−51	21	15	443	6.57
	L	Posterior cingulate	−9	−54	9	96	5.33
	L	Superior temporal gyrus	−60	3	6	22	4.61
	R	Superior temporal gyrus	57	−27	0	40	4.54
	R	Parahippocampal gyrus	−36	−33	−21	26	4.15
Adolescents	L	Postcentral gyrus	−57	−9	21	21	4
	L	Middle temporal gyrus	−60	−45	3	346	5.7
	L	Inferior frontal gyrus	−48	24	0	169	5.58
	L	Superior frontal gyrus	−18	21	48	54	4.97
	L	Middle temporal gyrus	−54	−6	−18	22	4.66
	R	Fusiform gyrus	48	−36	−9	56	4.59
Adults	L	Inferior parietal lobule	−45	−72	42	77	4.5
	L	Precentral gyrus	−54	−9	42	32	4.17
	L	Middle temporal gyrus	−60	−48	−3	256	5.69
	L	Inferior frontal gyrus	−45	30	−15	49	4.9
	R	Parahippocampal gyrus	24	−12	−24	28	4.82
	R	Superior temporal gyrus	57	0	3	44	4.53
	R	Middle temporal gyrus	54	−15	−15	59	4.49
	L	Superior parietal lobule	−36	−75	48	38	4.47
	L	Inferior temporal gyrus	−57	−9	−24	32	4.45
	L	Precuneus	−3	−63	33	102	4.42
	L	Superior temporal gyrus	45	−60	30	22	4.07

$P(\text{FDR corrected}) < 0.01$, $k = 20$.

Abbreviations: *k*, cluster size; L, left hemisphere; R, right hemisphere.

of all electrodes was below 20 k Ω . The few electrodes with high impedances (<1.5% between 40 and 60 k Ω) nonetheless delivered reliable EEG signals [Ferree et al., 2001].

Ocular artefacts were removed using an independent component analysis (ICA) [Jung et al., 2001] on 0.3–30 Hz filtered data. Prior to averaging, the corrected files were digitally bandpass filtered (1–30 Hz, 24 dB), down sampled to 256 Hz, and epoched from −125 ms pre- to 1,125 ms post-stimulus. Artefacts exceeding ± 80 μV (children: ± 100 μV) in any channel were automatically rejected. ERPs were transformed to the average reference [Lehmann and Skrandies, 1980] for all subsequent analyses. Separate group averages for adults, adolescents, children (pooled over noise and no-noise background) of the word and symbol string conditions were computed. The N1 amplitude analyses were conducted by computing the mean amplitude in the interval around the GFP (global field power, a time varying measure of map amplitude computed as the spatial root mean square; [Lehmann and Skrandies, 1980]) peak (± 30 ms) for each group average over words and symbol strings. The different mean latencies of the GFP N1 peak resulted in slightly different N1 intervals for the three age groups: (children: 197–257 ms, adolescents: 150–210 ms, adults: 146–206 ms, see Figure 1 and Figure 2). The mean GFP values of these intervals and the mean amplitudes at the occipito-temporal electrodes O1', O2' (placed 15% laterally to Oz) were used for subse-

quent analyses. Since children often have much larger amplitudes than adolescents or adults, we ensured that diminishing word-specificity could not exclusively reflect such developmental scaling, and analyzed also relative N1 amplitudes, which were group-wise normalized over both conditions and hemispheres (O1', O2') to a mean of 1. Overall age effects were thereby eliminated, but amplitude modulations between conditions and hemispheres preserved.

Scalp ERP Statistics

To examine developmental and condition-specific changes in laterality, a MANOVA with the within subject factors hemisphere (left: O1', right: O2'), condition and between subject factor age group was computed. To separate age and reading skill related changes we used a partial regression analyses of the word-specific (words vs. symbol strings) amplitudes at O1', O2' and GFP. As control variables for this analysis, we either used age or reading skills (reading speed in the local pseudoword reading test).

ERP Source Computations

ERP sources were determined by using standardized low resolution electromagnetic tomography (sLORETA) [Pascual-Marqui, 2002]. sLORETA is based on an appropri-

Figure 2.

Maps (left) of the group grand averages for the potential fields (μV) in the N1 interval for words and symbol strings. t -Maps show the t -values of the statistical difference between the potential field maps to words and symbol strings. Maps and t -maps are shown for children (top), adolescents (middle), and adults (bottom). The distinct difference in N1 amplitude and topography between words and symbol strings is highly consistent as evident in the t -maps. The statistical comparison of the sLORETA source activity (non-normalized) to words and to symbols

revealed regions with stronger sources for each group in the occipito-temporal cortex to words (word-specific activity) in the N1 interval. Regions coloured in red exhibit t -values corresponding to a $P < 0.01$ corrected for multiple comparisons. Adolescents, due to the smaller group size exhibited less occipito-temporal activation, however when lowering the threshold to $P < 0.05$ (corrected) a similar activation pattern as in children and adults was found (not shown here).

ately standardized version of the minimum norm current density to achieve exact localization. The SNR (set to 100 in the present study) is used for the standardization process and reflects an estimation of the proportion of signal power and noise variance in the data. A high SNR (e.g., 10–100) states a high signal power/noise variance as usual for averaged ERPs.

For source computations, potentials from EOG electrodes were excluded since they can cause localization errors due to non-uniform sampling of scalp potentials [Gottselig et al., 2004]. First, the sources were computed for every single subject for the word and the symbol string conditions separately for (i) the N1 time-range (according to mean amplitude analyses) and (ii) the whole stimulation duration (0–700 ms). Then paired statistical comparisons (second level random effect statistics) were conducted by using statistical non-parametric mapping (SnPM) (variance smoothing = 0.5), which corrects for multiple comparisons at all 6,239 voxels, to illustrate the difference between the

sources to words and the sources to symbol strings for each group separately again for the short (N1: see Fig. 2) and the long (0–700 ms: see Fig. 3C) interval.

fMRI Recording and Processing

fMRI was performed on a 1.5 T scanner (Intera, Philips Medical Systems, Best, The Netherlands). The visual stimuli were projected on a screen to match the visual parameters of the EEG session. The participants viewed the screen via a mirror located just above their eyes. The entire fMRI session lasted approximately 1.5 h. For functional imaging, 28 axial slices covering the whole brain were acquired with a blood oxygenation level dependent sensitive echo planar imaging sequence (TR = 3 s, TA = 2.57 s, TE = 55 ms, matrix = 64×64 ; interleaved slice acquisition, slice thickness = 5 mm; no interslice gap; flip angle = 90° , FOV = 220×220 mm) for a total of 215 (with reading: 262) scans. The first 3 scans were discarded to allow for

Figure 3.

A: fMRI analysis showing word activation (words vs. baseline) for each group at the corrected threshold of $P(\text{FWE}) < 0.05$, $k = 20$. **B:** Word-specific activation (words–symbol strings) is illustrated for each group at $P(\text{FDR}) < 0.01$, $k = 20$. **C:** The statistical comparison of sLORETA source estimations to words

and symbol strings (non-normalized) revealed regions (red) with stronger sources to words ($P < 0.01$ corrected) in the time-range from 0 to 700 ms for each group. The axial slices in A and B are illustrated at the corresponding activation maxima.

equilibration effects. A high resolution ($1 \times 1 \times 1$ mm voxel size, 100 slices) structural data set was acquired using a standard 3-D T1-weighted FLASH sequence.

No individual run had more than half a voxel maximum displacement in x -, y - and z -plane. Data were pre-processed and analyzed using the standard SPM5 procedure (Wellcome Department of Cognitive Neurology, London; <http://www.fil.ion.ucl.ac.uk/spm>) (spatial realignment to the first image, normalization using a 7th degree spline interpolation method to match the functional images with the Montreal Neurological Institute (MNI) template, spatial smoothing with a 9 mm full width at half maximum isotropic Gaussian kernel, the event-related modeling of activation (words with/without noise and symbol strings with/without noise) with the standard SPM hemodynamic response function, high-pass filter with a cut-off period of 512 s. Global scaling was performed to remove global signal drifts across individual time-series. Events were contrasted against rest blocks pooled over noise breaks, no noise breaks and null events. Activated brain structures were identified by transforming the MNI coordinate system of SPM5 into the standard brain atlas of Talairach and Tournoux [1988] using the Talairach Daemon software [Lancaster et al., 2000]. Studying developmental alterations in brain activity requires a common stereotactic space (MNI) for the analysis of children, adolescents and adults. Even though differences in the variability and location of brain structures have been found between children aged

7–8 y and adults, those anatomical differences are minor and do not negatively affect functional image comparison between children and adults [Burgund et al., 2002; Kang et al., 2003]. As our children were on average 10 y old, even smaller differences would be expected as in [Burgund et al., 2002; Kang et al., 2003], justifying the usage of the same adult template for image normalization of all groups.

FMRI Statistics

Condition effects were determined by random effect analyses. A full factorial ANOVA with factors age group and condition (pooled over noise and no noise) was computed with SPM5 using the individual contrast images smoothed at 9 mm. To minimize false positives and false negatives, p -values were corrected for multiple comparisons using either the false discovery rate (FDR) correction [Genovese et al., 2002] or the more stringent family wise error (FWE) correction.

Region of Interest Analyses for sLORETA and fMRI

For the VWFS gradient analyses, five spherical (radius = 6 mm) ROIs according to our previous article (see Brem et al. [2006] and Fig. 4) were chosen to examine the maturation of basic visual processing areas and differences

Figure 4.

A: Plots illustrating the normalized sLORETA mean activity to words (red) and symbol strings (blue) in the five analyzed left hemispheric ROIs within the VWFS, in the time range from 0 to 700 ms. ROI1 (R1) represents the most posterior, R5 the most anterior ROI. The activity is more pronounced to words in all anterior ROIs and age related decreases of word activity characterize the most posterior ROI (R1). **B:** fMRI ROI analyses corresponding to the ROIs chosen for sLORETA analyses. Clearly

recognizable is the gradient of the relative increase in word-specific activity from posterior to anterior ROIs. In contrast to ERP analyses, the overall activity to symbol strings (blue) is more pronounced than to words (red), especially in posterior ROIs. No age related changes in activity were found. At the bottom two pictures illustrate the location of the five ROIs used for sLORETA (bottom view) and fMRI (sagittal slice) analyses.

between conditions more closely. The ROIs covered the putative VWFA of the left fusiform gyrus and adjacent areas along a posterior–anterior axis: ROI 1 (MNI: $-42, -80, -14$), ROI 2 (MNI: $-42, -68, -16$), ROI 3 (= VWFA proper, MNI: $-42, -54, -17$), ROI 4 (MNI: $-42, -42, -18$) and ROI 5 (MNI: $-42, -30, -20$). ROI 3 represented the centre of the putative VWFA as described [Cohen et al., 2000] in the mid-fusiform gyrus.

For both, the sLORETA and fMRI ROIs, a MANOVA with the within-subject factors condition and ROI, and the

between-subject factor age group was computed. Further, a partial regression analyses was computed to determine age and reading skill specific changes of word-specific sLORETA ROI activity by controlling either for age or reading skills.

sLORETA

The mean sLORETA activity for each subject in each of the five (left hemispheric) ROIs was determined for the

word and symbol string condition separately over the whole stimulus presentation duration (0–700 ms) to have a better comparison with the time-insensitive fMRI measures. The MANOVA was computed once without and once with group-wise normalized (group mean over ROIs and conditions = 1) data, to eliminate the major effect of age in correspondence to N1 amplitude analyses.

fMRI

The individual percent signal change computed (MARSBAR, Version 0.41 [Brett et al., 2002]) for words and symbol strings in the five spherical ROIs on unsmoothed data was used for statistical analyses, thereby excluding effects of blurring through smoothing.

RESULTS

Behavior

Pseudoword reading speed and accuracy in the local reading test correlated negatively ($r = -0.28$, $P < 0.05$), indicating that subjects who read faster also made fewer mistakes. Further, pseudoword reading speed increased with age ($r = 0.64$, $P < 0.001$).

Average overall accuracy (>91%) and average accuracy to target stimuli (>78%) were high in both conditions, sessions and all groups (see Supporting Information Table I). Main effects of condition indicated that subjects responded faster ($F(1,46) = 10.74$, $P = 0.002$) and more accurately ($F(1,46) = 116.8$, $P < 0.001$) to words than to symbol strings. Main effects of age were found for reaction time (RT) ($F(2,46) = 12.1$, $P < 0.001$) and accuracy ($F(2,46) = 5.79$, $P = 0.006$). Post-hoc tests showed that children had significantly longer reaction times than adults (words, symbol strings: RT both $P < 0.001$) and adolescents (RT words ($P < 0.001$), symbol strings ($P = 0.008$)). Children performed worse than adolescents (target accuracy words ($P = 0.045$), symbol strings ($P < 0.003$)), while no difference was found between adolescents and adults. Neither accuracy nor RT differed significantly between sessions or methods (EEG, MRI).

ERP

Scalp amplitudes

N1 mean amplitudes at O1', O2' and GFP with and without normalization. The MANOVA with within subject factors condition, hemisphere, and between subject factor age group indicated (i) a general decrease in N1 amplitudes with age ($F(2,47) = 5.5$, $P = 0.007$), (ii) more pronounced occipito-temporal negativities to words than symbol strings ($F(1,47) = 78.6$, $P < 0.001$) and (iii) a diminishing condition difference with age ($F(2,47) = 25.1$, $P < 0.001$) (see Figs. 1 and 2 and SM Fig. 2). The condition difference ("tuning") in the N1 was more pronounced for the

left than right hemisphere ($F(1,47) = 8.0$, $P = 0.007$), in all three groups. The GFP confirmed the prominent amplitude reductions of the N1 with age ($F(2,47) = 18.6$, $P < 0.001$) and the more pronounced activity to words than symbol strings ($F(1,47) = 54.3$, $p < 0.001$) diminishing with age ($F(2,47) = 34.4$, $P < 0.001$).

The statistical results for the normalized data largely corresponded to the results of the non-normalized analyses except that the age main effect was eliminated through the normalization (details for the normalized results see SM).

Regression of N1 amplitude with age and reading skills. Since no difference was obtained for the regression analyses of non-normalized and normalized data, only the correlation coefficients and P-values of non-normalized results are reported. Partial regression analyses of the non-normalized and normalized N1 amplitudes pointed to a general decrease of the word-specific N1 amplitude at O1' ($r = 0.47$, $P = 0.001$), O2' ($r = 0.46$, $P = 0.001$) and GFP ($r = -0.47$, $P = 0.001$) with age, when controlling for differences in reading skills (see Fig. 5B). However, the word-specific N1 amplitude did not correlate with reading skills, when controlling for age.

sLORETA Sources

sLORETA sources of the N1 interval

The sLORETA source localization for word-specific activation in the N1 interval pointed to sources ($P < 0.01$) in the left occipito-temporal cortex in all three age groups and are illustrated in Figure 2. Note that due to the smaller group size, the sLORETA sources for adolescents are less pronounced. However when lowering the significance threshold to $P < 0.05$ (corrected), the estimated sources were at similar locations as for children and adults (not shown).

sLORETA sources 0–700 ms

The sources ($P < 0.01$) over the whole time range analyzed were strongly dominated by the N1 activity as illustrated in Figure 3C. Similar to the sources in the N1 time range, the maxima were in the left occipito-temporal cortex for each group.

sLORETA region of interest (ROI) analyses of the normalized mean activity within the 5 ROIs along the VWFS in the left hemisphere resulted significant main effects of condition ($F(1,47) = 38.1$, $P < 0.001$) and ROIs ($F(4,44) = 13.0$, $P < 0.001$), pointing to generally higher activity to words than symbol strings in more posterior as compared to anterior ROIs. The interaction of condition and ROIs ($F(4,44) = 7.0$, $P < 0.001$) indicated that the difference in activity between words and symbol strings was less pronounced in posterior than in anterior ROIs. The triple interaction of condition, ROI and age group ($F(8,90) = 2.5$, $P = 0.018$ (Pillai's Trace)) (see Fig. 4A) and the interaction of ROI $\times$ age group ($F(8,90) = 3.4$, $P = 0.002$ (Pillai's

Figure 5.

Partial regression plots showing (A) the decrease in word-specific activity (% signal change fMRI) with increasing reading performance (speed) in ROI2, independent of age; (B) the decrease in word-specific N1 amplitudes with increasing age, while controlling for reading (speed).

Trace)) achieved significance. Posthoc *t*-tests, examining the condition differences for each ROI and each age group pointed to more pronounced word than symbol string activity in all ROIs in children (R1: $P = 0.013$, R2: $P = 0.006$, R3: $P = 0.002$, R4/5: $P = 0.001$) but only in the four anterior ROIs in adolescents (R1: $p = 0.29$, R2: $p = 0.028$, R3: $p = 0.003$, R4/5: $p = 0.001$) and adults (R1: $p = 0.54$, R2: $p = 0.005$, R3/4: $p = 0.001$, R5: $p < 0.001$). The MANOVA for non-normalized sLORETA ROI largely confirmed the latter analyses and is described in the SM in more detail.

sLORETA activity in all ROIs neither correlated with reading skills, when controlling for age nor with age when controlling for reading skills.

fMRI

Figure 3 illustrates word (A) and word-specific (B: word-symbol strings) activation, for each group. The location of the overall cluster maxima are listed in Table I and Supporting Information Table II, as an overview. Regions, in which words elicited significantly more activity than symbol strings were predominantly found in the left hemisphere in all groups (see Fig. 3B). Note that no word-specific activation was found in the VWFS despite the distinct activation when contrasting words to baseline in the left VWFS. The lack of word-specific activation in the VWFS could not be explained by blurring the differences due to the smoothing kernel of 9 mm, as the same analyses with less smoothing (5 mm) yielded similar results and no word-specific activation in the VWFS (due to their similarity, results of the additional analyses are not shown).

ROI analyses

The MANOVA with within subject factors ROI (ROI 1, 2, 3, 4, 5), condition and between subject factor age group revealed a main effect for ROI ($F(4,47) = 60.4$, $P < 0.001$), thereby indicating increasing overall activity from anterior to posterior ROIs. The differential activation between conditions changed ($F(4,44) = 9.9$, $P < 0.001$) along the VWFS, whereby words showed more pronounced amplitudes in anterior ROIs, while the activity to symbol strings was most pronounced in posterior ROIs. This pattern remained similar for all three age groups (see Fig. 4B).

Regression of ROI activity with age and reading skills. The significant correlation of fMRI activity in ROI 2 with reading skills ($r = -0.34$, $P = 0.016$), when controlling for age indicated a reduction of word-specific activity with increasing reading speed (see Fig. 5A).

DISCUSSION

This sequential ERP and fMRI study focused on correspondences and discrepancies in the developmental alterations within the VWFS, as detected with the temporal sensitivity of ERPs and the high spatial resolution of fMRI, from childhood to adulthood.

As expected, reading performance, measured as pseudo-word reading speed increased with age. Accordingly children needed more time to detect repeated target stimuli than the older subjects in the one-back repetition detection task. The overall shorter reaction time and higher accuracy to word than symbol targets indicated that words

were easier to memorize than strings of meaningless symbols.

Convergence and Dissociation of fMRI and ERP Data on Word-Specificity

The comparison of the developmental patterns of the VWFS using fMRI and ERP yielded converging but also dissociating results.

Words evoked larger amplitudes than symbols over the left occipito-temporal cortex around 150–250 ms, consistent with coarse word-specific N1 specialization [Bentin et al., 1999; Maurer et al., 2005; Schendan et al., 1998; Tarkiainen et al., 1999]. The sLORETA sources of this word-specific ERP activity during the N1 as well as integrated over the whole presentation duration (700 ms) localized to the left occipito-temporal cortex for all three groups, showing that the word N1 strongly dominates the activity within first 700 ms of information processing in this implicit reading task. ROI analysis of the ERP sources along the posterior–anterior axes in the VWFS confirmed that integrated activity to words was higher than to symbol strings. In contrast, whole brain fMRI analyses did not point to word-specific activity within the VWFS, rather, words and symbols seemed to activate this region to a similar degree in the left hemisphere [Price et al., 1996; Tagamets et al., 2000; Turkeltaub et al., 2003]. Moreover, there was no evidence for a more medial activation of the symbol condition as compared to words (SM Fig. 3A) in the occipito-temporal cortex as reported in the study of Vinckier [Vinckier et al., 2007]. Only post hoc region of interest analysis on unsmoothed data along the posterior–anterior axes of the VWFS [Brem et al., 2006; James et al., 2005; Vinckier et al., 2007] pointed to a minor, relative increase in fMRI activity to words over symbols towards anterior regions. However, while the gradient in sLORETA for both the N1 and the integrated 700 ms time window was dominated by the increased activity to words as compared to symbols in all ROIs except for the most posterior one, the fMRI ROI activity was dominated by the activity to symbols, particularly in posterior ROIs. This dissociation of fMRI and ERP activity might directly reflect the different impact of attentional and modulatory top-down processes on ERPs and fMRI activation. Our results parallel the findings of the combined MEG and fMRI study of Furey [Furey et al., 2006] on face processing in that ERPs, similar to MEG responses are more sensitive in reflecting rapid, transient activity such as the N1, while the occipitotemporal fMRI response may be dominated by the re-entrant and more sustained activity introduced through task demands and top-down processes. The pronounced fMRI activation to symbol strings may therefore directly reflect that memorizing these unfamiliar strings is more difficult than memorizing words, as indicated by the behavioral results. As a consequence, the modulatory effects of top-down processes [Vinckier et al., 2007] probably cover earlier processing differences. Consequently, fMRI is not sensitive enough to

catch transient activity [Furey et al., 2006; Parviainen et al., 2006] such as the N1 and thereby highlights different aspects of information processing.

Development of Word-Specificity in the VWFS

N1 amplitudes and sources showed the typical developmental decrease with age [Brem et al., 2006; Holcomb et al., 1992; Taylor, 1993] while the spatial fMRI activation pattern of word processing already closely resembled the network found in adults as in previous studies [Church et al., 2008; Gaillard et al., 2003; Turkeltaub et al., 2003]. Although physical factors such as increasing skull thickness and decreasing skull conductivity could contribute to a developmental ERP attenuation, EEG and MEG activity (which is insensitive to skull properties) reductions with development parallel each other [Takeshita et al., 2002], suggesting that skull development plays a minor role after age six, and occipitotemporal N1 activity reductions in this age range primarily reflect increasing functional efficiency of neural networks [Parviainen et al., 2006].

The developmental decrease in the word-specific N1 can not be attributed to a general activity reduction with age as normalized N1 amplitudes corroborated it. The partial regression analyses clarify that increasing age rather than improving reading performance is responsible for the diminishing word-specificity in the N1. Together, these results strongly suggest that the N1 word-specificity in normal readers reflects a process which is either more important in beginning readers such as phonological decoding, or requires more resources due to being less automatized and specialized in children than in more practiced readers. Despite the major limitations in spatial resolution of the sLORETA procedure especially with close-by and deep sources [Wagner et al., 2004] caused by blurring, statistical differences emerged when comparing the estimated activity among the five ROIs along the posterior–anterior axes. The analyses of normalized and non-normalized sLORETA source activity showed that the activity is generally higher in posterior parts of the VWFS and most pronounced in children, pointing to further tuning of the VWFS by narrowing specialized word processing down to the anterior parts after childhood. The corresponding gradient of word-specific fMRI activity was already established in children and did not change with age as opposed to the sLORETA activity in the same regions. Whether this can be explained by top-down processes obscuring changes in transient fMRI activity needs to be clarified in future studies. Unlike the age-sensitive N1 amplitude and sLORETA activity, the fMRI response in the posterior VWFS was sensitive to reading performance. This negative correlation of reading speed and posterior word-specific activity suggests more focal, anterior word-specific activity in good readers.

To summarize, the dissociation of the present ERP and fMRI results strongly suggests that fMRI is more sensitive to task-specific top-down modulation [Vinckier et al., 2007]. Even though attentional effects have been reported

in ERP studies as early as the N1, those were minor as compared to effects on later ERP components [Bentin et al., 1999; Nobre et al., 1998]. Our results imply that the fine tuning of low level processing areas in specific brain areas might be better captured with time-sensitive brain imaging techniques such as ERPs and/or MEG. It therefore seems especially important to combine these different methods to investigate maturation of specific networks, as important aspects in information processing would remain undiscovered when using only one imaging technique. While our separate recordings revealed how the developmental sensitivity of the mean response differs among methods, simultaneous recordings might also uncover how trial-to-trial variability develops.

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