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Impact of literacy on the functional connectivity of vision and language related networks

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ABSTRACT

Learning to read leads to functional and structural changes in cortical brain areas related to vision and language. Previous evidence suggests that the Visual Word Form Area (VWFA), a region devoted to the recognition of letter strings in literate persons, acts as an interface between both systems. While different studies have performed univariate analyses to study the effects of literacy on brain function, little is known about its impact on whole functional networks, especially when literacy is acquired during adulthood. We investigated functional connectivity in three groups of adults with different literacy status: illiterates, ex-illiterates (i.e., who learned to read during adulthood), and literates (i.e., who learned to read in childhood). We used a data-driven, multivariate whole brain approach (Independent Component Analysis [ICA]) combined with a region of interest (ROI) analysis in order to explore the functional connectivity of the VWFA with four ICA networks related to vision and language functions. ICA allowed for the identification of four networks of interest: left fronto-parietal, auditory, medial visual and lateral visual functional networks, plus a control right fronto-parietal network. We explored the effects literacy on the connectivity between the VWFA and these networks, trying furthermore to disentangle the roles of reading proficiency and age of acquisition (i.e., literacy status) in these changes. Results showed that functional connectivity between the VWFA and the left fronto-parietal and lateral visual networks increased and decreased, respectively, with literacy. Moreover, the functional coupling of the VWFA and the auditory network decreased with literacy. This study provides novel insights in the mechanisms of reading acquisition and brain plasticity, putting to light the emergence of the VWFA as a bridge between language and vision. Further studies are required to characterize the interplay of proficiency and age of reading acquisition, and its relevance to models of brain plasticity across lifespan.

1. Introduction

Learning to read leads to the development of novel interactions between the cerebral mechanisms of vision and language (Dehaene and Cohen, 2007). The so-called visual word form area (VWFA), an associative visual area located in the left ventral occipito-temporal cortex, acts as an interface between high-level vision and language (Cohen et al., 2000, 2002), allowing for the propagation of orthographic information from

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the visual to the phonological and semantic systems. The specialization of the VWFA for reading results at least in part from preferential long-distance anatomical connectivity to perisylvian language areas (Bouhali et al., 2014; Chen et al., 2019), a feature already present before the acquisition of reading (Saygin et al., 2016). Reciprocally, literacy causes a further improvement of anatomical connectivity in the posterior segment of the left arcuate fasciculus, an important pathway connecting inferior temporal cortex and perisylvian language areas (Thiebaut de Schotten et al., 2014).

Reading acquisition induces functional changes in the primary visual cortex, in the ventral visual pathway including the VWFA, and in language areas, especially the dorsal auditory-motor system (Dehaene et al., 2015). Those changes, which correlate with reading proficiency (Dehaene et al., 2010; Thiebaut de Schotten et al., 2014), occur when literacy is acquired during childhood, but also when it is acquired during adulthood (Carreiras et al., 2009), although some differences have been reported (Dehaene et al., 2010). As the age of reading acquisition and the eventual reading proficiency are highly correlated, it may be challenging to isolate the respective correlates of those two factors in activation patterns.

Literacy also increases the exchange of information between vision and language. Thus, word reading activates language areas in proportion to reading proficiency (Dehaene et al., 2010). Reciprocally, in the absence of any visual stimulation, the VWFA of literate subjects is activated in a top-down manner during attentive speech listening (Yoncheva et al., 2010) and auditory lexical decision (Dehaene et al., 2010). Moreover, literacy is associated with changes in the responses of language areas to spoken input (Dehaene et al., 2010; Perre et al., 2009; Turkeltaub et al., 2003), and consequently, with the remodeling of speech processing abilities. Thus, illiterate subjects are poor at repeating pseudowords (Castro-Caldas et al., 1998; Petersson et al., 2000; Reis and Castro-Caldas, 1997), possibly due to the development of explicit phoneme-level representations of speech in literates (Morais et al., 1979).

A few fMRI studies used univariate functional connectivity analyses to assess the effects of literacy on the interactions between distant regions of interest. Functional connectivity methods are based on the measure of activity correlation across distant brain regions, allowing to infer patterns of synchronization and to delineate functional networks (Friston, 1994). Thus in literate adults, reading performance correlates with the connectivity between regions of interest located in the VWFA and in language regions including Broca's area and inferior parietal cortex (Koyama et al., 2011). Furthermore, the functional connectivity between the VWFA and the dorsal attention regions increases with age (Vogel et al., 2012), and the strength of functional connectivity between the VWFA and Wernicke's area at rest predicts performance in a semantic classification task (Stevens et al., 2017). Finally, in a group of adult illiterates who underwent literacy training, low-level visual areas showed an increase in functional connectivity with subcortical midbrain structures (Skeide et al., 2017).

However, the brain is organized into multiple and overlapping functional networks (Smith et al., 2009) whose properties cannot be fully captured using univariate functional connectivity methods such as seed-based functional connectivity (Xu et al., 2013), which cannot separate the mixture of the different source signals that may exist within the same brain region. In this respect, Independent Component Analysis (ICA) is a powerful data-driven analytical approach that performs multivariate decomposition of fMRI dataset (Fox and Raichle, 2007; Xu et al., 2013), allowing for the identification of major connectivity networks in the brain (or 'intrinsic connectivity networks') (Filippini et al., 2009; Seeley et al., 2007; Smith et al., 2009). A set of intrinsic connectivity networks characterized by low frequency oscillations (<0.1 Hz) and reflecting the standard functional architecture of the brain have been reproducibly observed using ICA during resting and active states (Beckmann et al., 2005; Cole et al., 2014; Laird et al., 2011; Smith et al., 2009; Tavor et al., 2016).

Therefore, the main goal of the present study was to explore the effect of literacy acquisition on the functional connectivity of the VWFA with intrinsic connectivity networks. Moreover, we will attempt to clarify in as much as possible whether the changes in the reading network induced by literacy depend of literacy status (i.e., age of reading acquisition) or on eventual reading proficiency, two factors which have naturally strong negative correlation. To this end, we performed functional connectivity analyses of fMRI data acquired in three groups of participants matched in socio-economic status, but with different degrees of literacy: an *illiterate group* (adults who did not attend school and never learned to read), an *ex-illiterate group* (adults who learned to read during adulthood by attending adult literacy courses), and a *literate group* (adults who attended school and learned to read in childhood). Activation results were reported in a previous study (Dehaene et al., 2010). A measure of reading proficiency was collected for each participant. ICA combined with dual regression was applied to fMRI data in order to isolate the networks of interest, and we measured the functional connectivity between the VWFA and each of those networks. Among the full repertoire of previously described functional networks (Beckmann et al., 2005; Laird et al., 2011; Smith et al., 2009), we focused the analyses on four networks of interest with an essential role in vision- and language-related functions (Laird et al., 2011; López-Barroso et al., 2015): a left lateralized fronto-parietal network (*left fronto-parietal network*) which covers dorsal language-relevant areas such as Broca's area, the inferior parietal cortex and Wernicke's area; a network comprising bilateral superior temporal gyrus, including primary auditory areas and Heschl's gyrus (*auditory network*); an occipito-parieto-temporal network mostly involving associative visual areas including the fusiform gyrus (*lateral visual network*); and an occipital network comprising primary visual areas (*medial visual network*).

Our most straightforward prediction was that the connectivity between the VWFA and the left fronto-parietal network should increase with literacy. A second prediction was that as the VWFA develops specific reading-related properties, it should become more dissimilar from and less correlated with other high-level visual areas in the lateral visual network. Moreover, in our tentative effort at disentangling the role of age of acquisition and proficiency, we predicted that connectivity changes associated with literacy, be they positive or negative, should follow one of two distinct profiles depending on the respective role of age of acquisition and of proficiency. If neural changes occur only whenever learning occurs early on and do not depend on proficiency *per se,* illiterates and ex-literates should not differ among them; and they should both differ from literates. Conversely, if connectivity only depends on proficiency, there should be monotonic change from illiterates to ex-literates and literates.

2. Materials and methods

2.1. Participants

Thirty Brazilian participants took part in this study. Neuroimaging data was acquired in the Brasilia unit of the SARAH Network of Neurorehabilitation Hospitals. All subjects were right-handed (Edinburgh handedness test, Oldfield, 1971), had normal or corrected-to-normal visual acuity, normal audition, and reported no neurological diseases. Participants gave their written informed consent to participate in the study (the consent form was read aloud and explained to illiterates). The participants were divided into three groups according to their literacy status:

Illiterate group. The illiterate group (n = 10, mean age: 53.3±6.8 years) comprised participants from rural areas (5 subjects) or urban centers in the Brasilia vicinity. Participants were illiterate for social reasons, with no history of any cognitive difficulty other than the lack of access to schools. The families of all these participants were originally from rural areas, and their parents had been illiterate rural workers.

Ex-illiterate group. Members of the ex-illiterate group (n = 9, mean age: 49.4±10.4 years) had the same background as those of the illiterate group, with very little or no access to early education. However, they attended adult reading courses and reached the criterion of a basic reading ability (to read correctly at least a few words).

Literate group. The literate group (n = 11, mean age: 55.1±4.5 years) comprised participants from the same community and socio-economical status as the illiterate and ex-illiterate groups but with 2–7 years of early education that resulted in the early acquisition of reading.

Notice that participants in the illiterate, ex-illiterate and literate groups belonged to the same social communities and occupational classification (natural resources, construction and maintenance). No differences in age were found between groups (Supplementary Methods). Thus, restricted comparisons involving these three groups are highly controlled. Further demographical data for the individual participants is reported in Table 1, and additional discussion on the literacy status of the participants is reported in the Supplementary Methods.

2.2. Behavioral test

To obtain a measure of reading ability, participants were asked to read aloud 36 Portuguese words (12 simple, 12 complex and 12 irregular) and 16 readable pseudowords (8 simple and 8 complex). The pseudowords were created changing the first phoneme of real Portuguese words. A more detailed description of the stimuli used is reported in the supplementary material of Dehaene et al. (2010).

As a measure of reading proficiency, we used the reading fluency score, i.e., the average between the number of words and pseudowords that could be read correctly per minute. For illiterates, who failed to identify even some single letters, reading proficiency was in all the cases 0. Table 2 reports individual reading fluency scores and group means for word and pseudoword reading accuracy as well as for word and pseudoword reading fluency.

2.3. fMRI acquisition

Functional sequences were acquired on a 3-T whole body system (Siemens Trio, Germany) using a gradient-echo planar imaging sequence sensitive to brain oxygen-level dependent (BOLD) contrast (40 contiguous axial slices, 3 mm thickness; TR = 2400 ms; Flip angle = 81°, TE = 30 ms, in-plane resolution = 3 × 3 mm, matrix = 64 × 64). Auditory stimuli were presented via high-fidelity stereo headphones (MR Confon).

Table 1
Demographical data.

Group	Age	Gender	Early education (<18)	Profession
Illiterate	50	F	1	Housewife
	52	F	0	Housewife
	48	F	0	Housemaid
	55	M	0	Street vendor
	62	M	0.9	Construction worker
	61	F	0	Housewife
	64	F	0	Housewife
	51	M	0.1	Rural worker
	47	M	0	Rural worker
	44	M	0.1	Public servant
Ex-illiterate	59	F	0	Housewife
	31	M	0	Construction worker
	42	M	0	Electrician
	61	M	0	Construction worker
	51	M	0	Construction worker
	39	F	0	Housewife
	60	M	0.2	Taxi-driver
	47	F	3	Housemaid
	55	F	1	Dressmaker
Literate	51	F	7	Housemaid
	60	F	5	Housewife
	53	F	6	Unemployed
	49	F	7	Housemaid
	58	M	4	Construction worker
	53	M	5	Construction worker
	55	M	4	Construction worker
	58	F	5	Dressmaker
	63	M	2	Rural worker
	49	M	7	Yardman
	55	M	6	Yardman

Since we were interested in discovering the changes that literacy induces in the permanent functional coupling between brain regions, the functional connectivity analyses reported in this article only concerns the slow fluctuations (<0.1 Hz) that characterize the intrinsic connectivity networks (Fox and Raichle, 2007; Seeley et al., 2007). Although the functional dataset analyzed in this study included four auditory lexical decision runs comprising 135 brain images each, lexical decision trials occurred at a frequency of 0.3 Hz, and all neural phenomena driven by the activation task were therefore outside the range of frequencies studied here (see Fig. S1). In any case, we avoided using images acquired while subjects were reading to assure any potential influence of the task-related activity that could bias our results. Indeed, correlations between distant regions observed during reading could be attributed to task-evoked synchronization, which could differ between literacy groups due for example to different engagement in the task, rather than to differences in the structure of intrinsic connectivity. This concern can be addressed by using resting-state imaging or, as we did, images acquired during an auditory task. The analysis of the lexical decision activations in the same subjects as reported in the current study has been previously reported in Dehaene et al. (2010). A full description of the task is provided in the Supplementary Method.

2.4. fMRI preprocessing and independent component analysis

We used ICA, a data-driven approach, to delineate the intrinsic connectivity networks that were comprised of visual and language-related brain regions. Fig. 1 depicts an overview of the workflow. ICA analysis was performed using Probabilistic Independent Component Analysis (Beckmann and Smith, 2004) as implemented in Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) version 3.14, part of FMRIB's Software Library (FSL, www.fmrib.ox.ac.uk/fsl).

Individual functional data pre-processing was carried out with FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL. Four runs per subjects were preprocessed with FEAT analysis. The preprocessing consisted of head motion correction using MCFLIRT (Jenkinson et al., 2002); non-brain-removal using BET (Smith, 2002); spatial smoothing by using a Gaussian kernel of FWHM 5 mm; grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor; and high-pass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 50.0 s). Each subject's run was registered to that subject's high-resolution structural image and then registered to the MNI152 template by using affine (FLIRT; Jenkinson et al., 2002; Jenkinson and Smith, 2001) and non-linear registration (FNIRT; Andersson et al., 2007; Jenkinson et al., 2012).

To identify the set of intrinsic connectivity networks common to all subjects, preprocessed functional data from the whole sample (n = 30) was then temporally concatenated to create a single 4D data set (Fig. 1A). This approach allows identifying common spatial patterns across subjects. The following preprocessing was applied to the 4D input dataset: masking of non-brain voxels; voxelwise de-meaning of the data; and normalization of the voxelwise variance. Pre-processed data were whitened and projected into a 40-dimensional subspace using Principal Component Analysis. The whitened observations were decomposed into sets of vectors which describe signal variation across the temporal domain (timecourses), the session/subject domain, and across the spatial domain (maps) by optimizing for non-Gaussian spatial source distributions using a fixed-point iteration technique (Hyvärinen, 1999). Estimated component maps were divided by the standard deviation of the residual noise and thresholded by fitting a mixed model to the histogram of intensity values (Beckmann and Smith, 2004).

Table 2
Reading performance in terms of accuracy and reading fluency.

Group	W fluency	PW fluency	Difference W-PW	Average fluency	W % correct	PW % correct	Average correct
Illiterate	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
	0	0	0	0	0	0	0
Ex-illiterate	7	6	1	6.5	55.6	43.8	49.7
	8	8	0	8	47.3	56.5	51.9
	16.5	19	−2.5	17.75	91.8	100	95.9
	20.5	17	3.5	18.75	100	100	100
	39.5	**29.5**	**10**	**34.5**	**97.2**	**100**	**98.6**
	42	**35**	**7**	**38.5**	**94.4**	**93.8**	**94.1**
	50	**34.5**	**15.5**	**42.25**	**94.4**	**87.5**	**91**
	49	**38**	**11**	**43.5**	**94.4**	**87.5**	**91**
	55	**35.5**	**19.5**	**45.25**	**94.4**	**100**	**97.2**
Literate	**29**	**23**	**6**	**26**	**100**	**100**	**100**
	42.5	**33**	**9.5**	**37.75**	**97.2**	**100**	**98.6**
	41.5	**36.5**	**5**	**39**	**97.2**	**100**	**98.6**
	46.5	**38**	**8.5**	**42.25**	**100**	**100**	**100**
	57.5	47.5	10	52.5	91.7	87.5	89.6
	64	51.5	12.5	57.75	94.4	75	84.7
	67	57	10	62	75.0	81.3	78.1
	77	53.5	23.5	65.25	97.2	100	98.6
	93	64.5	28.5	78.75	94.4	100	97.2
	96	64.5	31.5	80.25	100	100	100
	139.5	99	40.5	119.25	100	100	100
Mean I	0	0	0	0	0	0	0
Mean E-I	31.89	24.72	7.22	28.31	0.86	0.85	0.85
Mean L	68.5	51.6	16.86	60.07	0.95	0.95	0.95

W: word; PW: pseudoword. I: illiterates; E-I: ex-illiterates; L: literates.

2.5. *Dual-regression*

Between-subject analysis of the fMRI data was performed using a regression technique (Dual Regression, Filippini et al. (2009)) in order to explore differences between subjects. Dual regression approach identified subject-specific temporal dynamics (Fig. 1B) and spatial maps (Fig. 1C) that are associated with each whole group-ICA component (i.e., the individual version of each component). This implies: using the full set of unthresholded ICA spatial maps (derived from the whole sample) in a linear model fit (spatial regression) against the separate fMRI datasets, resulting in matrices describing the temporal dynamics for each component and subject; and using these time-courses in a linear model fit (temporal regression) against the associated fMRI dataset to estimate subject-specific spatial maps. Then, the distinct component maps were collected across subjects into single 4D files (1 per each component, with the four dimension being subject identification) for further analysis.

Within the 40 networks obtained with ICA on the whole dataset, we identified the common intrinsic connectivity networks, and among them, we selected the networks of interest. Thus we focused our analysis on 4 networks (Fig. 1D): the left fronto-parietal network, the auditory network, the lateral visual network, the medial visual network; plus a control right fronto-parietal network. The selection procedure was performed by visual inspection and by using spatial correlation against a set of templates previously reported (Smith et al., 2009), which is a common method in ICA studies (Clewett et al., 2014; Cowdrey et al., 2014; Filippini et al., 2009). The selection of the networks was based on their strong implication in language and visual functions, covering regions classically related to them and which fit well our hypothesis. The medial visual network covers the whole medial occipital cortex, including the primary visual areas in the calcarine sulcus, the lingual gyrus, the ventral part of the precuneus, and the lateral geniculate nucleus of the thalamus. This network supports the first stages of visual processing, including of letter strings. The lateral visual network covers higher-level associative visual areas, extending laterally from the occipital pole, both into the ventral temporal lobe (including the VWFA), and dorsally into occipito-parietal cortex. The left fronto-parietal network is strongly left lateralized and includes mainly dorsal brain areas implicated in language phonological/language processes (Laird et al., 2011), such as inferior parietal and frontal areas plus a cluster in the ventral left occipito-temporal region. The regions covered in this network have been related to reading (Laird et al., 2011), vocabulary acquisition (Mechelli et al., 2004), access to semantics (Vigneau et al., 2006), working memory (Ravizza et al., 2004) as well as comprehension and syntactic processes (Friederici, 2011). However, although the left fronto-parietal network includes frontal areas that may respond to linguistic stimuli, it also covers regions of the parietal cortex that may be more generally engaged in goal-directed behaviors (Fedorenko and Thompson-Schill, 2014). This point and the fact that this network did not cover the superior temporal cortex, which plays an important role in the language functions, motivated us to include the auditory network in our analyses. The auditory network covers bilaterally the primary and secondary auditory cortices in the superior temporal gyrus, including the Heschl's gyrus and the planum temporale. This network has been related to the initial stages of speech perception and auditory word learning (Hickok and Poeppel, 2007; López-Barroso et al., 2015). Finally, a control right fronto-parietal network, for which we expect no effect of literacy, was included in order to rule out non-specific effects of literacy on the functional brain. The right fronto-parietal network has been implicated in reasoning functions, attention and memory (Laird et al., 2011).

Notice that up until this point, the data processing (ICA and dual

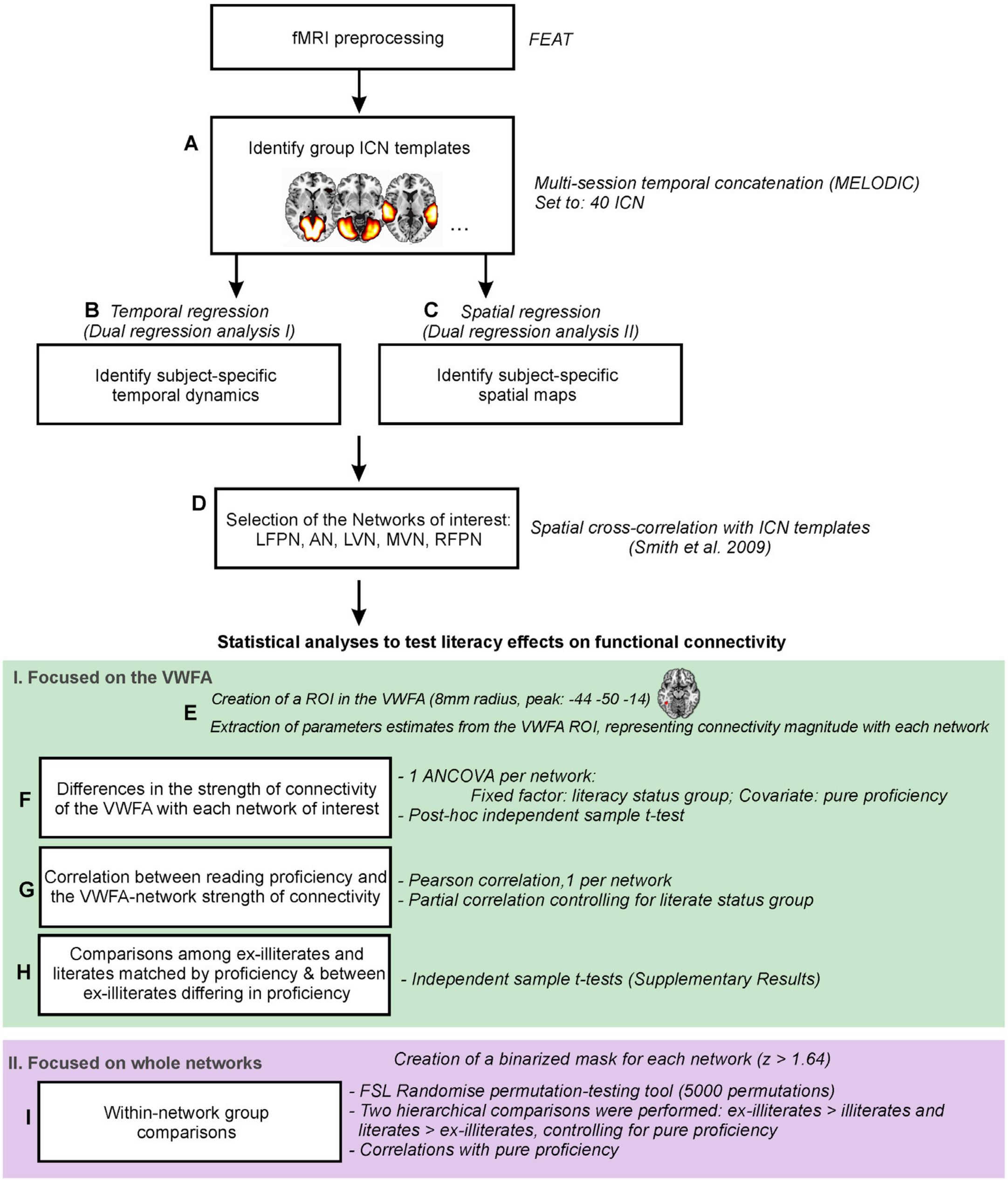

Fig. 1. Flow chart of the Independent Component Analysis (ICA), dual regression and statistical approaches used in this study. After preprocessing, group ICA was performed in order to extract 40 independent components (**A**). Temporal and spatial regressions were performed with Dual Regression in order to identify the subject-specific temporal dynamics (**B**), and spatial maps (**C**). Five out of forty retrieved networks were selected as networks of interest based on their relation with language, auditory or vision processes (**D**), and statistical analyses were performed. A ROI approach was combined with dual regression output in order to extract the connectivity magnitude between the VWFA and the networks (**E**). Then, a set of analyses were performed to evaluate the effects of literacy on the connectivity between the VWFA and each network (**F**, **G**, **H**). Finally, differences in connectivity within each network were explored with randomise (**I**). ICN: intrinsic connectivity networks; LFPN: left fronto-parietal network; AN: auditory network; LVN: lateral visual network; MVN: medial visual network; RFPN: right fronto-parietal network; ROI: region of interest; VWFA: visual word form area.

regression) has been performed on the full dataset without taking into account the literacy group membership.

2.6. Differences in functional connectivity of the VWFA and the networks of interest

For each participant, we extracted the parameters estimates from a ROI in the left ventral occipito-temporal cortex, corresponding to the location of the VWFA (Fig. 1E). The ROI was defined as a sphere (8 mm radius) centered on coordinates MNI -44 -50 -14. These coordinates represent the main peak of activation resulting from the contrast written sentences vs. rest in the same group of participants (previously reported in Dehaene et al., (2010)). This approach has been used in previous publications, in which ROIs were derived either from comparisons of ICA networks between groups (Binnewijzend et al., 2012; Clewett et al., 2014; Cowdrey et al., 2014; Mostert et al., 2016; Sanefuji et al., 2017; Zamboni et al., 2013) or from independent functional activation data gathered in the same subjects (Besseling et al., 2013). For each participant, parameter estimates were extracted, representing the functional connectivity magnitude between the VWFA ROI and each network. Parameter estimates were obtained from the maps produced by dual regression (stage II), and averaged across all voxels within the ROI (Zamboni et al., 2013). These values reflect the coherence of the ROI's time-course with the time-course of the entire network. This procedure is equally valid for all networks, irrespective of their topographic relationship with the VWFA. Outliers, defined as individuals whose value was 2 standard deviations above or below the mean of their group (i.e., illiterate, ex-illiterate, literate), were removed for the analysis (1 in the VWFA-left fronto-parietal network analysis; 1 in the VWFA-high level visual network analysis; 1 in the VWFA-low level visual network analysis and 1 in the VWFA-auditory network analysis).

For each network, we carried out 3 analyses: First, a one-way ANCOVA comparing functional connectivity magnitude between literacy status groups for each network, while controlling for 'pure proficiency' (Fig. 1F). Pure proficiency was defined as the residual of reading proficiency (i.e., average of the number of words and pseudowords read per minute) after regressing out literacy status. Second, Pearson's correlations between functional connectivity and reading proficiency (Fig. 1G). Note that Pearson's correlation is an appropriate coefficient for zero-clustered data (Huson, 2007; Pegado et al., 2014a; Thiebaut de Schotten et al., 2014), as it is the case of reading proficiency (i.e., reading proficiency of illiterates is 0 since they could not read a single word or pseudoword). Third, partial correlations between functional connectivity and reading proficiency, while controlling for literacy status.

In the supplementary Results, we report additional analyses comparing ex-illiterates and literates while decorrelating inasmuch as possible age of reading acquisition (i.e., literacy status) and reading proficiency (Fig. 1H). For that, we compared: (1) literate and ex-illiterate participants matched in proficiency; and (2) ex-illiterates participants differing in proficiency. All details on the formation of samples are provided as Supplementary Results.

2.7. *Differences in functional connectivity within networks of interest*

Finally, we performed an analysis of functional connectivity with no a priori focus on the VWFA, looking for voxels whose functional synchronization with the networks of interest was modulated by literacy status (Fig. 1I). For that, we used voxel-wise non-parametric tests as implemented in the FSL Randomise permutation-testing tool (Winkler et al., 2014). Analyses were constrained to voxels within a binarized mask defined by the thresholded networks of interest (threshold: $z > 1.64$) (Clewett et al., 2014). Pure reading proficiency was introduced as a covariate in the model. A total of 5000 permutations were performed and significant clusters were corrected for multiple comparisons using threshold-free cluster enhancement (TFCE, Smith and Nichols, 2009). Results are reported at $p < 0.05$, corrected. First, group comparisons were performed using a two-sample unpaired *t*-test. Two hierarchically ordered comparisons were performed for each network: ex-illiterates minus illiterates; and literates minus ex-illiterates while controlling for proficiency. Second, we looked for regions whose functional connectivity with each network was positively correlated with pure proficiency.

3. Results

3.1. *Identification of the functional networks of interest*

Probabilistic ICA produced a total of 40 independent components representing group-averaged networks of brain regions. To identify the four networks of interest, each component from our dataset was spatially cross-correlated with the templates of resting state networks reported by Smith et al. (2009). This approach successfully identified the left fronto-parietal (crosscorrelation with the left fronto-parietal network template: $r = 0.65$), the auditory (crosscorrelation with the auditory network template: $r = 0.56$), the medial visual (crosscorrelation with the medial visual network template: $r = 0.53$), and the lateral visual (crosscorrelation with the lateral visual network template: $r = 0.74$) functional networks (Fig. 2A). The right fronto-parietal 'control' network was also identified (crosscorrelation with the right fronto-parietal network template: $r = 0.53$) (Supplementary Fig. S2A). Importantly, across the whole brain, the left ventral occipito-temporal cortex, where the VWFA is located, was the only region of overlap between the lateral visual (covering high-level visual regions) and left fronto-parietal networks (Fig. 2B).

3.2. *Differences in functional connectivity of the VWFA and the networks of interest*

A set of ANCOVA analyses controlling for pure proficiency were performed (Fig. 3). The functional connectivity of the VWFA with the left fronto-parietal network showed a main effect of literacy status ($F(2,25) = 3.53$, $p = 0.045$) as well as a monotonic increase from illiterates to ex-illiterates to literates (linear effect: $p = 0.014$). Post-hoc tests showed that connectivity was stronger in literates than in illiterates ($p = 0.014$), while ex-illiterates stood in-between, not differing from the extreme groups (ex-illiterates vs. illiterates: $p = 0.11$; literates vs. ex-illiterates: $p = 0.36$). Connectivity of the VWFA with the auditory network differed only marginally between groups ($F(2, 25) = 2.68$, $p = 0.088$), but showed a significant linear effect ($p = 0.045$). Post-hoc tests showed that the literates had a lower connectivity than the illiterates ($p = 0.045$) and marginally lower than the ex-illiterates ($p = 0.085$), who did not differ between them ($p = 0.85$). For the lateral visual network, no group effect was found ($F(2, 25) = 2.67$, $p = 0.089$), but there was a monotonic decrease from illiterates to ex-illiterates to literates (linear effect: $p = 0.03$). Post-hoc tests showed that connectivity was stronger in illiterates than in literates ($p = 0.03$), while ex-illiterates stood in-between, not differing from the extreme groups (illiterates vs. ex-illiterates: $p = 0.33$; ex-illiterates vs. literates: $p = 0.21$). The strength of connectivity between the VWFA and the medial visual network was weak and did not differ across groups ($F(2, 25) = 2.67$, $p = 0.39$; linear effect: $p = 0.17$). Finally, no group effect was found for the control network ($F(2, 26) = 0.39$, $p = 0.68$; linear effect: $p = 0.9$) (Supplementary Fig. S2B).

In addition, we computed the correlation between the connectivity of the VWFA with each network and reading proficiency (Fig. 3B). This showed that reading proficiency was positively correlated with the connectivity between the VWFA and the left fronto-parietal network ($r = 0.41$, $p = 0.026$), while it was negatively correlated with the connectivity between the VWFA and the lateral visual network ($r = -0.43$, $p = 0.017$). No significant correlation was found between reading proficiency and the connectivity between the VWFA and the medial visual network, the auditory network or the control network (all $p > 0.19$) (Fig. 3B and Supplementary Fig. S2C). Finally, all correlations between proficiency and connectivity disappeared if controlling for literacy status using partial correlations (all $p > 0.4$). In summary, we found that with higher literacy, the functional connectivity of the VWFA increases with the left fronto-parietal network, and decreases with the auditory and the lateral visual networks.

The previous analysis was based on two strongly correlated parameters that distinguish ex-illiterates from literates: age of acquisition, as summarized by literacy status, and actual reading proficiency. Although groups differed strongly in average reading proficiency (Dehaene et al., 2010), within-group variability allowed for some overlap in individual proficiency across groups (see Table 2). This allowed us to perform ancillary analyses to disentangle the effects of proficiency and literacy status by comparing samples of literate and ex-illiterate participants selected on the basis of their proficiency (see Supplementary Results). In summary, despite their limited statistical power due to the small size of samples (Turner et al., 2018), these analyses suggest that changes in the connectivity of the VWFA with the left fronto-parietal network (and tendentially with the lateral visual network) are more dependent on actual proficiency (Supplementary Fig. S3). In contrast, the changes in

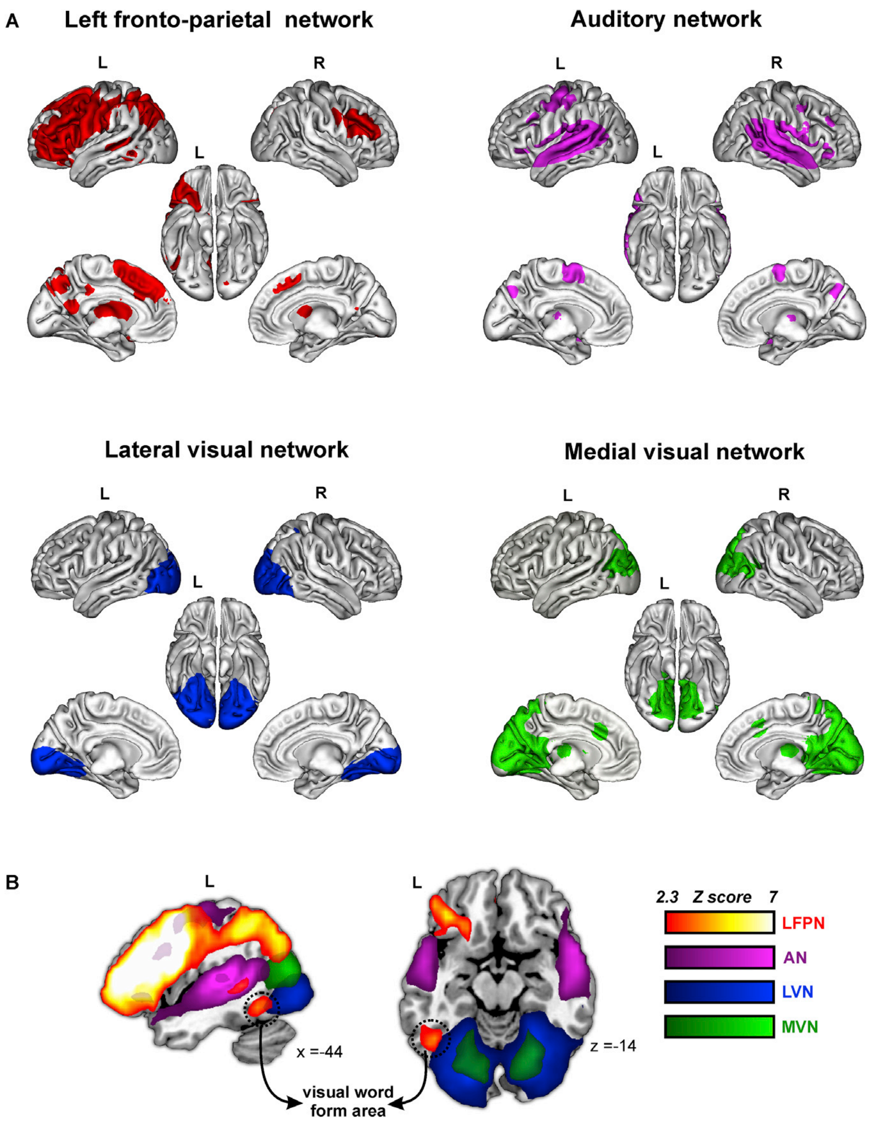

Fig. 2. Intrinsic connectivity networks of interest. **A.** Spatial group maps of the four networks of interest as identified with an independent component analysis covering all participants (illiterates, ex-illiterates and literates): left fronto-parietal network (LFPN); auditory network (AN); medial visual network (MVN); lateral visual network (LVN). **B.** Overlap of the four networks. The location of the VWFA, as identified with functional magnetic resonance imaging in the same subjects (Dehaene et al., 2010) (dotted circle). The VWFA is the only region belonging both to the LVN and to the LFPN networks. R: right hemisphere; L: left hemisphere.

connectivity with the auditory network seem to be rather a matter of age of acquisition (Supplementary Fig. S3).

3.3. *Differences in functional connectivity within networks of interest*

Finally, we performed an analysis of functional connectivity with no a priori focus on the VWFA, looking for voxels whose correlation with the networks of interest was modulated by literacy status while controlling for pure proficiency. A cluster in the left ventral occipito-temporal cortex, overlapping with the VWFA, showed greater functional connectivity with the left fronto-parietal network in literates than in ex-illiterates. This analysis revealed some other significant differences outside of the visual cortex, which are reported in Table 3A. In addition, for each network, regions in which functional connectivity was correlated with pure proficiency are reported in Table 3B.

4. Discussion

We studied the impact of literacy on the connectivity between the VWFA and intrinsic functional networks comprising areas associated to language and vision, the two core components of reading processes. Additional analyses were performed in an attempt to disentangle the respective role of age of acquisition and reading proficiency, two strongly correlated features of literacy.

In agreement with our predictions, the VWFA showed stronger connectivity with the left fronto-parietal network, and weaker coupling with the auditory and the lateral visual networks, in literates than in illiterates. This pattern prevailed both when comparing connectivity across groups of participants and when correlating connectivity with proficiency. Moreover, restricted analyses suggest that the connectivity of the VWFA with the left fronto-parietal network was dependent on individual reading proficiency, while the connectivity with the auditory network was more related to the age of reading acquisition. Finally, analyses without an a priori focus on the VWFA showed that literacy was associated to increased connectivity in the left ventral occipito-temporal cortex with the left fronto-parietal network.

4.1. *Connectivity of the VWFA with the language and lateral visual networks*

The functional connectivity between the VWFA and both the left fronto-parietal and the lateral visual networks was different between

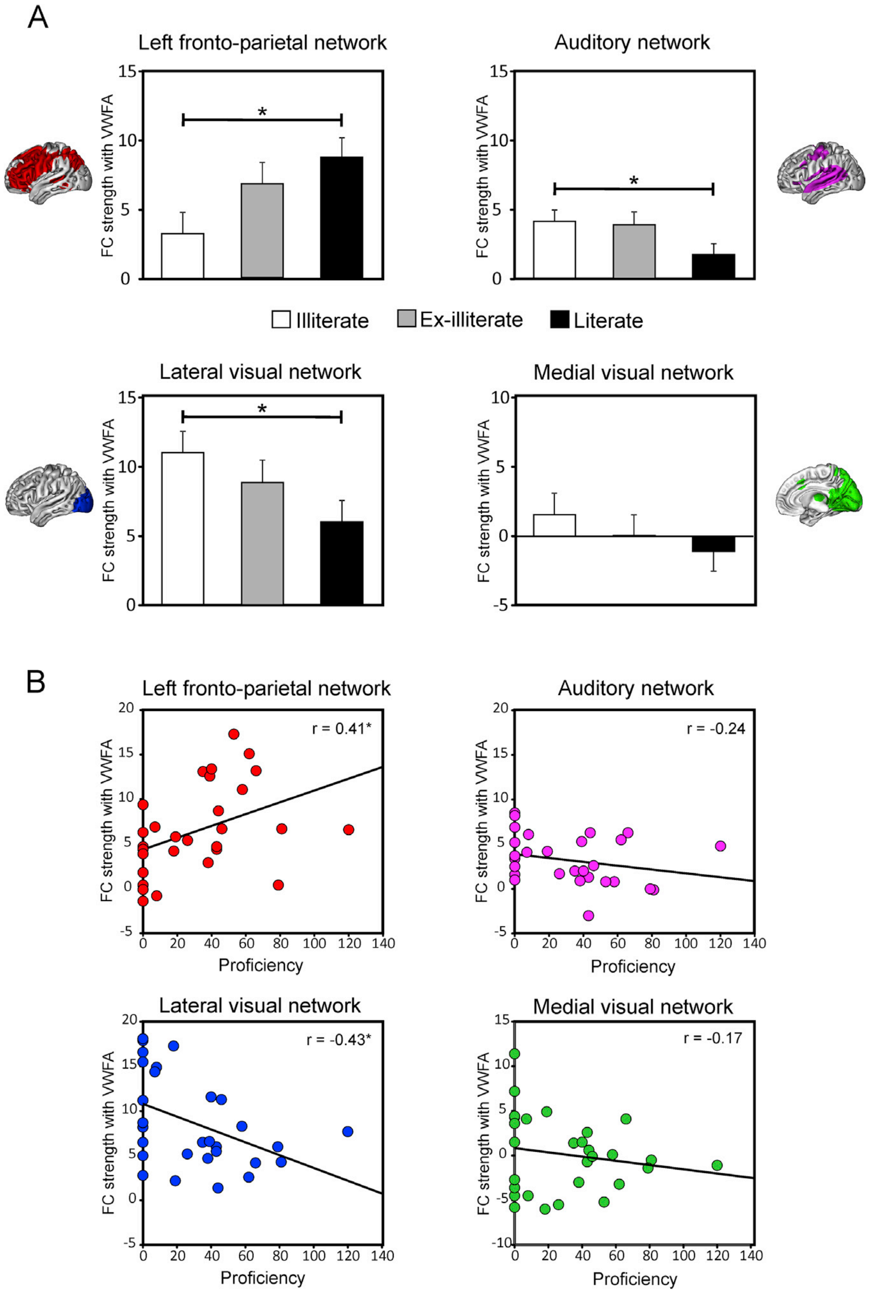

Fig. 3. Strength of functional connectivity between the VWFA and each network, as a function of literacy. A. Contrasts across groups showed differences in the functional connectivity of the VWFA with the left fronto-parietal network, auditory network and the lateral visual network when controlling for pure proficiency. **B.** Pearson's correlation analyses between functional connectivity magnitudes and reading proficiency. FC: functional connectivity; *$p < 0.05$.

literates and illiterates. In both cases, ex-illiterates stood in-between illiterates and literates. The intermediate position of ex-illiterates is in agreement with fMRI and EEG activation results reported by Dehaene et al. (2010) and Pegado et al. (2014a,b) in the same participants. The lack of statistical significance of the comparisons between the ex-illiterates and the other groups likely results from the overlap in proficiency across groups, particularly between literates and ex-illiterates. As shown in Table 2 (highlighted in bold), five of the 9 ex-illiterates outperformed the poorest literate, and 4 out of the 11 literates did not outperform the best ex-illiterate.

As proficiency was highly correlated with group membership, those patterns appeared both when correlating individual proficiency with connectivity irrespective of group membership (Fig. 3B), and in an ANCOVA between groups, even when controlling for within-group variability (Fig. 3A). Naturally, correlations between proficiency and connectivity vanished when regressing out group membership.

Supporting the importance of reading proficiency relative to group membership, Supplementary Results of selected participants showed that literates and ex-illiterates matched in proficiency did not differ (Fig. S3A), while ex-illiterates differing in proficiency differed in the functional connectivity of the VWFA with the left fronto-parietal network (Fig. S3B). There was similar but non-significant trend for the lateral visual network. One may speculate that these high level networks enjoy enduring plasticity, allowing for functional changes to occur at any age.

Table 3
Differences in functional connectivity within each network. A. Hierarchical comparisons between groups while controlling for pure proficiency. The VWFA (highlighted in bold) shows increased functional connectivity with the left fronto-parietal network in literates as compared to ex-illiterates. B. Brain areas showing increases in the strength of functional connectivity within each network with higher pure proficiency.

A. Literacy effects

	Ex-illiterates > Illiterates			Literates > Ex-illiterates		
	Brain regions	MNI	p-value	Brain regions	MNI	p-value
LFPN	L frontal pole	−30, 58, 8	0.027	L superior frontal gyrus	−22, 34, 44	0.016
	L superior parietal cortex	−34, −70, 44	0.024	L inferior frontal gyrus	−50, 10, 8	0.026
	L medial frontal cortex	−2, 34, −16	0.011	**L occipito-temporal cortex**	**−42, -54, 8**	**0.033**
AN	–	–	–	L posterior superior temporal gyrus	−66, −42, 8	0.003
	–	–	–	L precentral gyrus	−42, −2, 56	0.007
	–	–	–	R temporal pole	58, 10, −20	0.003
	–	–	–	L motor/premotor cortex	−54, −14, 48	0.047
	–	–	–	R precuneus	2, −58, 44	0.02
	–	–	–	R supramarginal gyrus	46, −42, 16	0.049
LVN	–	–	–	–	–	–
MVN	–	–	–	–	–	–
RFPN	R middle frontal gyrus	50, 18, 36	0.044	R middle frontal gyrus	46, 46, 28	0.016
				R frontal pole	50, 42, 16	0.048

B. Pure proficiency effects

	Brain regions	**MNI**	**p-value**
LVN	R inferior lateral occipital cortex	50, −70, 0	0.025
	R inferior lateral occipital cortex	38, −90, 0	0.05

Note: p values are FWE-corrected. LFPN: Left fronto-parietal network; AN: Auditory Network; LVN: Lateral visual network; MVN: Medial visual network; RFPN: right fronto-parietal network (control network); L: Left; R: Right.

Indeed, learning a second language yields functional (Perani et al., 2003) and structural (Li et al., 2014) changes in language areas all through life.

Increased coupling of the VWFA with the left fronto-parietal network.

With both ROI-based and whole-brain analyses, we showed that the coupling of the VWFA with inferior parietal and frontal cortices of the left fronto-parietal network increases with literacy. The purpose of all reading systems is to give access to meaning and sound of words from visual input. Indeed, a host of imaging studies in healthy subjects (Price, 2012) and of neuropsychological studies in brain-damages patients (Woollams et al., 2018) have established that beyond modality-specific processing, the comprehension of both auditory and written language rely on an identical set of common brain regions subtending lexico-semantic and phonological processes. Accordingly, as reviewed in the introduction, reading is associated with an increase in the cross-talk (Dehaene et al., 2010; Koyama et al., 2011; Skeide et al., 2017) and anatomical connectivity (Thiebaut de Schotten et al., 2014) between the occipito-temporal cortex and language areas. In agreement with those previous findings, we observed that the connectivity of the VWFA with the ICA-defined left fronto-parietal network increases with literacy.

Decreased coupling of the VWFA with the lateral visual network.

Our ROI-based analyses showed that the coupling of the VWFA with the lateral visual network decreases with literacy. Thus the lateral visual network and the left fronto-parietal network entertain very different relationships with the VWFA. While language areas are distant from the VWFA and establish novel links with it, the ventral occipito-temporal cortex may be seen as the background against which the VWFA specialization emerges. Two factors may explain the changes in the temporal pattern of activity of the VWFA. First, the VWFA of literate subjects develops reading-specific properties such as invariance for case and font (Dehaene et al., 2004; Qiao et al., 2010; Szwed et al., 2014), loss of mirror-invariance (Pegado et al., 2014b), or sensitivity to orthographic regularities (Vinckier et al., 2007). Such novel local properties, specific to the VWFA, make it functionally dissimilar from neighboring associative visual regions, including regions with a specialization for faces, houses, or body parts. Similarly to the VWFA, other areas in the visual cortex show both different sets of functional properties, and different patterns of long-distance functional connectivity (Hutchison et al., 2014). Second, the increased cross-talk between the VWFA and language areas may rely upon stronger driving of VWFA activity by language areas, through stronger temporal coupling (Engel et al., 2013). Overall, reading proficiency modifies the VWFA connectivity, by making it functionally closer to the language system, and more distinct from other associative visual areas that do not contribute to the reading process.

4.2. *Connectivity of the VWFA with the auditory network*

Literates showed decreased connectivity compared to both ex-illiterates and illiterates, whereas these two latter groups did not differ. In the context of reading, the functional links between letter reading and the auditory cortex have been scrutinized in a series of studies on cross-modal integration. Van Atteveldt and collaborators (van Atteveldt et al., 2010) showed that activation of the superior temporal cortex by vowel sounds increases when a matching printed letter is presented, while it is reduced by mismatching letters. This effect was robustly replicated, but it prevails only when sound and letter are exactly synchronous (Van Atteveldt et al., 2007), when subjects listen passively and do not perform an active matching task, and in languages with transparent letter-sound correspondences (Dutch as opposed to English) (Holloway et al., 2015). Moreover, the effect of congruency does not appear in dyslexic readers (Blau et al., 2009). Concerning audiovisual speech and multimodal object perception also, the superior temporal gyrus and superior temporal sulcus, both parts of our auditory network, are critical to cross-modal integration (Ghazanfar and Schroeder, 2006; Kilian-Hütten et al., 2017). It is thus possible that literacy-related changes in the connectivity between the VWFA and the auditory network relate to reading-specific tuning of cross-modal perception. However, the behavioral significance of those changes in connectivity may be limited. Indeed, bilateral superior temporal auditory cortices do not show reduced functional coupling with the VWFA in dyslexics relative to controls, suggesting a non-critical involvement in the functional development of the VWFA (Schurz et al., 2015; van der Mark et al., 2011; Zhou et al., 2015).

Analyses restricted to matched samples of participants (Supplementary Results) suggest that, contrary to the left fronto-parietal networks, age of acquisition, and not proficiency, is the best predictor of the connectivity between the VWFA and the auditory network. This suggests that when reading is acquired during childhood, the reading specialization of the VWFA leads to its decoupling from auditory areas. Indeed, letters do not represent the source of the corresponding sound, as opposed to the image of a face, which represents the source of a voice (Von Kriegstein and Giraud, 2006), pointing to a fundamental difference a the nature of cross-modal links in those two cases. When reading is acquired later in life, even if the VWFA can still synchronize with dorsal language areas and decouple from other associative visual areas, the functional decoupling from auditory areas may be irreversible.

4.3. Connectivity of the VWFA with the medial visual network

No difference was found in the functional connectivity between the medial visual network and the VWFA as a function of literacy. Indeed, while the VWFA changes its specialization pattern with the acquisition of literacy, it is equally involved in object perception irrespective of literacy. Thus in illiterates, faces and objects evoke intense activity in the region of the VWFA, a response which decreases with literacy, while response to words increases (Dehaene et al., 2010). In illiterates the VWFA may play an important role in the perception of faces and objects, requiring as much coupling with the medial visual network as in literate subjects. Importantly, despite this lack of change in coupling, low-level visual cortices undergo functional changes associated with reading acquisition (Dehaene et al., 2010; Pegado et al., 2014a). Similarly, other types of visual perceptual learning modifies the functional properties of early visual cortex, with no associated changes in long-distance functional connectivity (Schwartz et al., 2002).

4.4. Differences between ex-illiterates and literates

Literates and ex-illiterates differed in age of reading acquisition, but also in their amount of reading experience. The latter factor has a massive impact on reading proficiency (see for instance Aghababian and Nazir, 2000; Pourcin et al., 2016), and likely accounts for most of the average difference between our two groups. Literates and ex-illiterates were matched in socio-economic status, probably explaining that some literates had a limited practice of reading, and showed rather low performance, overlapping with that observed in skilled ex-illiterates.

When studying functional connectivity within intrinsic connectivity networks with no a priori focus on the VWFA, the broadest divide separated literate from ex-illiterate participants. They differed in both the language and the auditory networks, while ex-illiterate differed from illiterates only in the left fronto-parietal network. This divide may result from the overall age-related decrease in functional and anatomical plasticity (Burke and Barnes, 2006; Froudist-Walsh et al., 2018; Lebel and Beaulieu, 2011), but also from differences in reading strategies. Ex-illiterates may proceed like children with limited reading experience, who rely on the less efficient phonological reading route, serially converting graphemes into phonemes, before moving to automatic word recognition (Share, 1995, 2004). In contrast, literates, fitting with their high reading fluency, would mainly use the lexical route, allowing for a fast access to the semantic and phonological properties of words. This hypothesis is supported by the relative proficiency with pseudowords, which require phonological reading, and real words, which may be read through both routes. As shown in Table 2, the relation between fluency for words and for pseudowords changes with proficiency. The poorest ex-illiterates readers showed no difference between words and pseudowords, indicating that they were both deciphered through the same phonological route. In contrast, the three best readers showed an advantage of words over pseudowords of more than 30 items per minute, indicating that real words were processed through the fast and effective lexical route, unavailable for pseudowords. This correlate of proficiency parallels the emergence of an advantage for words over pseudowords which is observed in children during reading acquisition, for instance when comparing the performance of first graders between the months of January and June (Sprenger-charolles et al., 1998).

4.5. Strengths and limitations

In the present work we compared three groups of subjects, covering a broad range of reading proficiency. Importantly, they were recruited from the same community and did not differ in socio-economic status, a parameter known to impact cognitive abilities, school achievements and neural structures (Hackman et al., 2010; Jednoróg et al., 2012).

This study may show some limitations. First, our analysis was performed on fMRI data acquired during an auditory task and not during actual rest. We could nevertheless isolate the intrinsic connectivity networks based upon low-frequency synchronization independent from the current task. We expect that future studies using resting state with well-controlled samples like in the current study will replicate our findings. Second, when studying individuals with distinct histories of education, it is difficult to ensure that all possible motivational, socio-economic and cognitive parameters are perfectly matched (see Box 1 in Dehaene et al., 2015 for a discussion on methodological issues on literacy research). Nevertheless, we controlled carefully for socio-economic status, and we collected behavioral data (auditory lexical decision) during image acquisition. The three groups differed neither in their error rates, nor in their response latencies (see Supplementary Material in Dehaene et al., 2010) on this task. This supports the idea that groups did not differ in their mastery of at least the main aspects of oral language, and that our current results do not result from some difference in cognitive set between the groups during image acquisition. Finally, even if some analyses may be underpowered due to sample size (e.g., subgroup analyses), all analyses converge to support our conclusions.

Future studies including larger samples of ex-illiterates and literates are needed to accrue evidence on how literacy status, reading experience and reading strategy influence the functional organization of the reading brain, and to determine whether reading experience affects the brain in the same way throughout life and results in the same level of eventual reading proficiency.

4.6. Conclusions

To conclude, our results show that learning to read leads to changes in the functional connectivity between the VWFA and the functional networks involved in language, vision and audition. Literacy is associated with increased functional connectivity between the VWFA and the left lateralized fronto-parietal network, containing Broca's and Wernicke's areas; and decreased connectivity with the lateral visual network, containing mainly other associative (high-level) visual areas. These effects are evident for adult literates who learned to read during childhood compared to adult illiterates, while the intermediate position of ex-illiterates could be due to their limited practice of reading or to a lack of plasticity. Proficiency, rather than age of acquisition, seems to be the major correlate of brain connectivity, suggesting that the brain circuits which support reading are open to change at any age.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2020.116722.

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