Brain & Language 124 (2013) 45–55

Contents lists available at SciVerse ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Default-mode network functional connectivity in aphasia: Therapy-induced neuroplasticity

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ARTICLE INFO

Article history:
Accepted 7 November 2012

Keywords:
Aphasia
Default-mode network
Functional connectivity
fMRI
Neuroplasticity

ABSTRACT

Previous research on participants with aphasia has mainly been based on standard functional neuroimaging analysis. Recent studies have shown that functional connectivity analysis can detect compensatory activity, not revealed by standard analysis. Little is known, however, about the default-mode network in aphasia. In the current study, we studied changes in the default-mode network in subjects with aphasia who underwent semantic feature analysis therapy. We studied nine participants with chronic aphasia and compared them to 10 control participants. For the first time, we identified the default-mode network using spatial independent component analysis, in participants with aphasia. Intensive therapy improved integration in the posterior areas of the default-mode network concurrent with language improvement. Correlations between integration and improvement did not reach significance, but the trend suggests that pre-therapy integration of the default-mode network may predict therapy outcomes. Functional connectivity allows a better understanding of the impact of semantic feature analysis in aphasia.

1. Introduction

Mostly studied in the resting-state condition (e.g. Raichle et al., 2001), decreased activation in the DMN as compared to rest has also been reported during task performance (Binder et al., 1999; McKiernan, Kaufman, Kucera-Thompson, & Binder, 2003; Raichle et al., 2001; van de Ven, Esposito, & Christoffels, 2009). Our understanding of the DMN role is evolving. To date, two main hypotheses have been proposed. According to the Sentinel hypothesis, the DMN plays a role in attending internal and external stimuli, monitors the external environment, and supports diffuse attention (Buckner, Andrews-Hanna, & Schacter, 2008; Ghatan et al., 1995). The second hypothesis refers to its introspective function, linked to episodic memory (Greicius & Menon, 2004), attention and working memory (Sorg et al., 2007). From an anatomical point of view, this brain network includes the posterior cingulate cortex, the precuneus, median and the dorsolateral prefrontal cortices and the subgenual anterior cingulate cortex (Grecius et al., 2007; Mevel et al., 2010). Other brain areas reported to be part of the DMN include the inferior parietal cortex (McKiernan et al., 2003), the bilateral fusiform gyrus (McKiernan et al., 2003), the bilateral cuneus, and the left middle occipital gyrus (Christoff, Ream, & Gabrieli, 2004; McKiernan et al., 2003), the angular gyrus (Binder et al., 1999), the median temporal lobe (Christoff et al., 2004; Greicius & Menon, 2004), and the superior temporal cortex (Gould, Brown, Owen, Bullmore, & Howard, 2006).

According to Kelly, Uddin, Biswal, Castellanos, and Milham (2008), a higher DMN functional connectivity at rest would favors network efficiency. As well, decreased DMN connectivity has been associated to functional deficits in daily living (Davis et al., 2009), particularly in the anterior–posterior fiber tracts within the DMN (Andrews-Hanna et al., 2007; Sambataro et al., 2010), in accordance with the disconnection hypothesis. Hence, according to this hypothesis, reduced connectivity between the frontal and posterior areas of the DMN would result in cognitive impairment in the elderly. Moreover, other studies report age-related differences in frontal–occipital (Wang et al., 2010) and frontal–parietal (Meunier, Achard, Morcom, & Bullmore, 2009) connectivity. As for clinical populations, a disconnection between the prefrontal cortex and the hippocampus has been described in Alzheimer's disease (Grady, Furey, Pietrini, Horwitz, & Rapoport, 2001). Thus, the evi-

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http://dx.doi.org/10.1016/j.bandl.2012.11.004

dence suggests that connectivity studies between the anterior and posterior areas of the DMN might be particularly important for our understanding of the impact of disease on brain function (Zhang & Raichle, 2010).

As for language processing, a stronger deactivation of the DMN was observed during a speech production task, as compared to a speech listening task (van de Ven et al., 2009). Since speech production requires more active processing than speech listening, this evidence is consistent with previous functional connectivity studies showing that DMN activity decreases significantly during active processing as opposed to automatic processing (Binder et al., 1999). In addition, a stronger negative activity was found in younger adults during phonemic fluency than during semantic fluency (Meinzer et al., 2012), which lead the authors to conclude that the reduction of DMN activity is less pronounced in younger adults during more demanding cognitive tasks. To summarize, the literature suggests that the DMN activation is modulated by the degree of cognitive control required by the task (McKiernan et al., 2003; van de Ven et al., 2009).

Deficits in cognitive control can lead to naming impairments in aphasia (Jefferies, Patterson, & Lambon-Ralph, 2008). While the relationship between language and executive functions is complex, there has been evidence showing a correlation between executive functioning and language processing, including word retrieval (Baldo et al., 2004). Moreover, the patients with the higher executive functioning are the ones improving the most (Hinckley & Carr, 2001). In fact, cognitive control deficits are frequently expressed by an incorrect selection (i.e. paraphasias in aphasia), particularly when more than one response is competing, which requires cognitive control or intention. According to Heilman, Watson, and Valenstein (2003), intention is the ability to resolve this competition during the execution of an action. Also known as 'executive attention' (Fuster, 2003), intention mechanisms regulate processing of incoming information and affect neural processing during the execution of a task (Crosson et al., 2003). Given that trained tasks require less conscious control and cognitive effort (Mason et al., 2007), it is expected that the DMN activity during trained tasks will be diminished as compared to untrained tasks. Considering that previous studies have shown that the DMN is sensitive to fluctuations in performance (Greicius & Menon, 2004; Sorg et al., 2007), its investigation in chronic aphasia might shed light on language improvement—especially regarding the level of cognitive "engagement" following language therapy in aphasia.

In the present study, participants with aphasia received an intensive Semantic Feature Analysis (SFA) therapy (Boyle & Coehlo, 1995). SFA therapy allows the production of the semantic features of a specific word to higher its level of activation, which then allows more automatic word processing (Boyle, 2004). Investigating the DMN functional connectivity is also likely to be important in order to better understand the impact of a language therapy in chronic aphasia. Given that it has never been studied before, the study of the DMN has the potential to unveil important information regarding aphasia and its recovery.

The present study investigated functional interactions profiles of the DMN before and following language therapy in a group of participants with aphasia. We used a spatial independent component analysis (sICA) approach and functional integration measures. Functional integration is a global measure of connectivity within a network (Marrelec et al., 2008). This method has already proven its efficacy in detecting task difficulties in aphasia. Thus, Warren, Crinion, Lambon Ralph, and Wise (2009) found a positive correlation between the functional integration in the left and right superior temporal cortices and behavioral measures of single word and sentence comprehension in aphasia. Using the same type of analysis, Sharp, Turkheimer, Bose, Scott, and Wise (2010) showed an increased frontoparietal integration during language processing in patients who had recovered from aphasia. Similarly, healthy subjects exposed to difficult-listening conditions also showed increased frontoparietal integration.

The present study had two goals: (a) To gather data regarding the configuration of the DMN in participants with aphasia, and (b) to compare it to the DMN pattern observed in a group of elderly participants. Measures were taken while performing an oral naming task, and at two points in time: before and after intensive lexical training. The DMN was defined by reference to a canonical DMN spatial pattern, as observed in the healthy control and in line with previous literature. Considering that previous studies have shown that the DMN is sensitive to behavioral fluctuations (Greicius & Menon, 2004; Sorg et al., 2007), and given that automatic processing is reflected by an increase in integration values in the DMN (Binder et al., 1999), we hypothesize that language improvement following therapy will be associated with greater DMN functional connectivity. The second goal of this study is to characterize the dynamic interactions of the anterior and the posterior subnetworks of the DMN. In accordance with the disconnection hypothesis, we postulate that SFA will increase the functional integration between anterior and posterior areas.

2. Materials and methods

2.1. Participants

The study participants included a control group of 10 healthy participants (4 men and 6 women with a mean age of 70 ± 3.99 years) and nine participants with aphasia secondary to single left-hemisphere lesions (5 men and 4 women with a mean age of 62 ± 6.0 years). Fig. 1 shows the distribution of the brain lesions of the participants with aphasia. The demographics of the study participants are shown in Table 1. All participants were right-handed, native French-speakers. Potential subjects were excluded from the study if they had a history of psychiatric illness, a neurological disease, or metal implants not compatible with fMRI. Written informed consent was obtained prior to the experiment. Ethics Committee of the Regroupement de Neuroimagerie in Quebec approved the study.

2.2. Design

In order to compare the effect of a language therapy in chronic aphasia, healthy participants went through language training. Since there is evidence of similar cognitive mechanisms between re-learning ones' own language in aphasia and learning novel words for neurologically intact subjects (Cornelissen et al., 2004), healthy participants were enrolled on computerized lexical training of Spanish words (Raboyeau, Marcotte, Adrover-Roig, & Ansaldo, 2010). Thus, healthy participants had two fMRI scans: one 5 days after their training started (early learning phase), and one after 14 ± 1.15 training sessions (consolidation phase) when a success rate of 97% ± 6 was attained in naming the words. During each fMRI session, participants named, in Spanish and in French, the items they were shown. For a detailed description of this protocol, see Raboyeau et al. (2010). Functional connectivity analysis was performed at each time, for the French (mother tongue) naming condition.

The experimental protocol has been reported into detail in previous studies carried out by our research group (Marcotte & Ansaldo, 2010; Marcotte et al., 2012). To summarize two baseline language assessments, within a 1-week interval, were conducted prior to language therapy. The treated and untreated items were selected from the incorrectly named items during the two

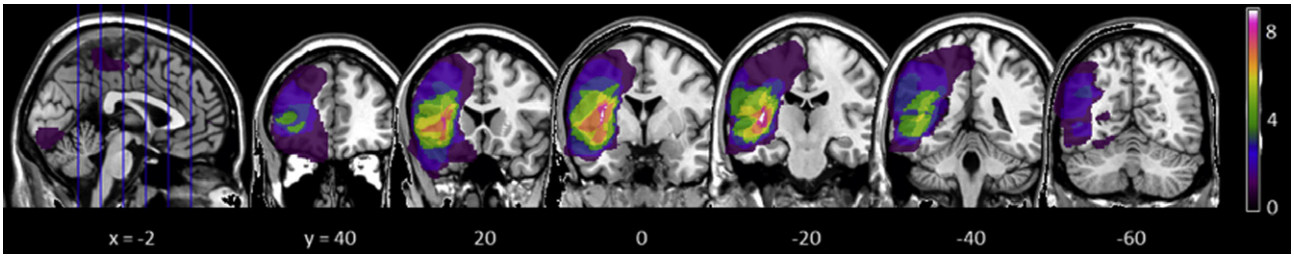

Fig. 1. Distribution of the lesion areas of all patients with aphasia, on a brain template. Color coding reflects the number of patients (1–9) with lesion overlap.

Table 1
Demographics of study patients and control subjects.

Patients	P01	P02	P03	P04	P05	P06	P07	P08	P09	
Age (years)	67	67	66	55	50	67	62	63	64	
Sex	M	M	M	M	F	F	M	F	F	
Scolarity (years)	20	15	12	12	12	12	17	22	12	
Time post-stroke (months)	72	54	241	61	65	300	72	77	50	
Lesion volume (cm^3)	167.84	117.84	84.77	14.55	64.16	172.21	118.39	295.76	215.31	
Aphasia and speech profile (according to MT-86)	Broca's aphasia	Broca's aphasia	Broca's aphasia	Broca's aphasia	Broca's aphasia	Broca's aphasia	Broca's aphasia	Wernicke's aphasia and AoS	Broca's aphasia and AoS	
Severity	Moderate	Moderate to severe	Moderate to severe	Moderate to severe	Severe	Severe	Moderate to severe	Severe	Severe	
Word retrieval deficits	Post-lexical	Post-lexical	Post-lexical	Post-lexical	Post-lexical	Post-lexical	Post-lexical	Semantic	Post-lexical	
Language training results										
Trained words (%)	100	85	80	90	80	90	80	60	60	
# Sessions	9	11	9	9	18	9	14	18	18	
Controls	C01	C02	C03	C04	C05	C06	C07	C08	C09	C10
Age (years)	66	68	70	71	71	80	72	66	69	69
Sex	F	F	M	M	M	F	F	M	F	F
Scolarity (years)	17	12	22	22	18	12	12	17	15	17
Lexical learning results										
Words learned (%)	96	100	96	97.5	97.5	92.5	92.5	100	94	99
# Sessions	16	25	25	28	23	29	42	21	23	16

AoS, Apraxia of speech.

baselines for all nine participants. Only words that were incorrectly named at the two baselines were included in the SFA therapy list, composed of 20 objects and their corresponding pictures. After the first fMRI session, participants with aphasia received SFA (Boyle & Coehlo, 1995). The therapy was given by a trained SLP for the duration of one hour three times a week. During each session, participants were trained on naming 20 objects and a series of semantic prompts corresponding to the semantic features of the target (Boyle & Coehlo, 1995) were given in form of a question for each word that the participant was unable to name. Before and after attaining a success rate of 80% or a maximum of 6 weeks, they underwent two fMRI sessions during which a naming task was performed.

2.3. Stimuli and procedure

Participants were trained for the task and procedure in the mock scanner. They were instructed to talk softly and speak with minimal head movements, jaws and body parts. Participants lay supine on the MRI scanner bed with their head stabilized by foam cushions to minimize global head motion during overt language production (Heim, Amunts, Mohlberg, Wilms, & Friederici, 2006). Moreover, regarding local motion related artefacts, given that these artefacts are concentrated in the temporo-polar and fronto-basal areas (Kemeny, Ye, Birn, & Braun, 2005), they do not concern the DMN areas included in the present study. During fMRI, the participants only had to do a naming task. They were shown either pictures or digitally distorted images of these pictures (control condition). Using presentation software v.10.0 (www.neurobs.com), pictures (stimuli) were projected, in random order, from a computer onto a screen at the head of the bore, and they were visible in a mirror attached to the head coil.

For both groups, the pictures were all presented in a single run. Each picture was presented for 4500 ms, with a randomized interstimulus interval of a minimum of 4500 ms to a maximum of 8500 ms, followed by a pale green interstimulus screen in order to mitigate the effects of periodic or quasi-periodic physiological noise. Participants were asked to name the pictures as accurately and quickly as possible and to say "baba" when presented with a distorted picture. An MRI-compatible microphone was placed in front of the participant's mouth, and oral responses were recorded using Sound Forge software (www.sonycreativesoftware.com). For the controls, 40 images were presented at both time points and a total of 220 scans were acquired. For the participants suffering from aphasia, 100 images were presented both before and after therapy and a total of 496 scans were acquired.

2.4. Imaging protocol

Images were acquired using a 3T MRI Siemens scanner with a standard 8-channel head coil. For the control subjects, the image sequence was a $T2^*$-weighted pulse sequence with time to repeat (TR) = 2000 ms, time to echo (TE) = 30 ms, matrix = 64 × 64 voxels, field of view (FOV) = 240 mm, flip angle = 90o, slice thickness = 4.5 mm, and acquisition = 28 slides in the axial plane, to scan the whole brain, including the cerebellum. A high-resolution

structural scan was obtained after the two functional runs using a 3D T1-weighted pulse sequence with TR = 1300 ms, TE = 4.92 ms, flip angle = 25°, 76 slices, matrix = 256 × 256 mm, voxel size = 1 × 1 × 1 mm, and FOV = 280 mm.

For the participants with aphasia, the parameters changed following a scanner upgrade. Thus, the scanner image sequence was a T2*-weighted pulse sequence with TR = 2200 ms, TE = 30 ms, matrix = 64 × 64 voxels, FOV = 192 mm, flip angle = 90o; slice thickness = 3 mm, and acquisition = 36 slides in the axial plane, with a distance factor of 25%, to scan the whole brain, including the cerebellum. A high-resolution structural scan was obtained before the two functional runs using a 3D T1-weighted pulse sequence with TR = 2300 ms, TE = 2.91 ms, 160 slices, matrix = 256 × 256 mm, voxel size = 1 × 1 × 1 mm, and FOV = 256 mm.

2.5. Preprocessing

Before network detection, preprocessing was performed using SPM5 and consisted of slice timing, realignment, and smoothing, using a spatially smoothed 10-mm Gaussian filter. Mean translation parameters of the three dimensions were below the fMRI voxel size of 3 × 3 × 3 mm^3, and no maximum values exceeded 3 mm in any direction. To reduce physiological noise, a retrospective estimation and correction of breathing and heartbeat was applied (Hu, Le, Parrish, & Erhard, 1995). A temporal cut-off (cut-off frequency 4.16×10^{-3} Hz) was applied to the functional data to filter out subject-specific low-frequency signal drifts.

2.6. Data-driven network detection and identification of the DMN

We applied an exploratory method based on spatial independent component analysis (McKiernan et al., 2003) of a single time series followed by a hierarchical clustering to gather spatially similar components across subjects, leading to group-representative classes. Group representative large-scale networks were extracted for each fMRI session and for both healthy controls and participants with aphasia using sICA (Perlbarg et al., 2008) as implemented in NetBrainWork (http://sites.google.com/site/netbrainwork/). First, the 40 spatial components explaining most of the variance in each control subject were extracted. In the group of participants with aphasia, given the heterogeneity of the group, 80 spatial components were extracted. These components were scaled to *z*-scores and registered to the Montreal Neurological Institute (MNI) standard space using nonlinear spatial transformations as implemented in SPM5. Then, based on their spatial similarity (Esposito et al., 2005), the components were clustered across the subjects of each group. Then, the definition of the group-representative classes was automatically processed. From these classes, fixed-effect group *t*-maps were computed and we used a threshold of $P < 0.05$ (uncorrected for multiple comparisons, to keep enough voxels to design the regions of interest). Within the large-scale network extracted, we visually identified the network exhibiting a spatial organization corresponding to the regions defined in the DMN (e.g. Binder et al., 1999; Christoff et al., 2004; Greicius & Menon, 2004; McKiernan et al., 2003; Mevel et al., 2010).

2.7. Region of interest selection

Our objective was to quantify the functional connectivity within the structures included in the data-emergent DMN in healthy controls. Accordingly, only the regions that were part of the DMN of the control subjects at both T1 and T2 were defined as region of interest (ROIs). The DMN was then composed of 16 ROIs (see Table 2), all of which have been previously reported as part of the DMN (e.g. Binder et al., 1999; Christoff et al., 2004; Greicius & Menon, 2004; McKiernan et al., 2003; Mevel et al., 2010). ROIs were defined using automatic detection, a procedure that consists of selecting the peaks of the group *t*-map as seed voxels. Then, the regions of interest are built from these peaks by using a region-growing algorithm that recursively added to the region the adjacent voxel with the highest *t*-score and stopped if there was no more significant surrounding voxels. The algorithm stopped when the region was attaining five voxels. Thus, all ROIs were composed of five significant voxels.

2.8. Hierarchical integration

Based on the disconnection hypothesis, we decided to examine the functional interactions within the anterior and posterior parts of the DMN as well as the integration between these subnetworks. To do so, we computed the inter-regional temporal correlations using hierarchical integration (Marrelec et al., 2008). Hierarchical integration establishes the degree of connectivity within a system itself and between systems (Marrelec et al., 2008). Integration does not assess pairwise interactions between its various components. It rather captures the global level of statistical dependence within a brain system. Briefly, hierarchical integration provides a global measure of functional information exchanges between time courses of BOLD signal recorded in the selected ROIs (Marrelec et al., 2008). In other words, hierarchical integration is a decomposition of the integration measure of the whole network introduced by Tononi (1994) in S subnetworks and between these subnetworks.

The functional connectivity between two regions is defined as the correlation between the time courses of these two regions. In our case, working with 16 regions within the DMN yields $[16] * ([16] - 1)/2 = 120$ correlation coefficients that form the correlation matrix $\mathbf{R}$. To summarize this information into one global measure of connectivity within the DMN, we resorted to a measure originating from information theory (Watanabe, 1960) and known in neurocomputing and neuroimaging as integration (Tononi, 1994; Marrelec et al., 2008). If $\mathbf{R}_{DMN}$ is the correlation matrix corresponding to the regions within the DMN, then the corresponding integration reads

$$I_{DMN} = -\frac{1}{2} \ln |\mathbf{R}_{DMN}|$$

where ln is the natural log function and $|\,|$ the determinant function. Integration is equal to zero if and only if all correlation coefficients are equal to zero; otherwise, it is positive. The more correlated the regions, the higher the integration, and a correlation of 1 corresponds to an infinite integration. Based on the disconnection hypothesis, we also examined separately the levels of integration within the anterior and posterior parts of the DMN (I_{ANT} and I_{POST}, respectively) as well as the interactions between both subnetworks ($I_{BETWEEN}$). I_{ANT} and I_{POST} are easily computed as

$$I_{ANT} = -\frac{1}{2} \ln |\mathbf{R}_{ANT}|$$

and

$$I_{POST} = -\frac{1}{2} \ln |\mathbf{R}_{POST}|$$

while $I_{BETWEEN}$ can be calculated as

$$I_{BETWEEN} = \frac{1}{2} \ln \frac{[|\mathbf{R}_{ANT}| + |\mathbf{R}_{POST}|]}{|RDMN|}$$

A key property of integration is that it is hierarchically additive, that is,

$$I_{DMN} = I_{ANT} + I_{POST} + I_{BETWEEN}$$

Table 2
Significant connectivity peaks in healthy elderly controls before and after lexical training.[a]

Control group: Default-mode network prior to therapy						Control group: Default-mode network after therapy					
Peak label	Peak MNI coordinates					Peak label	Peak MNI coordinates				
		Peak *t*-score	*x*	*y*	*z*			Peak *t*-score	*x*	*y*	*z*
Cerebellum II	**R**	**3.07**	**24**	**−83**	**−33**	Cerebellum II	R	2.95	21	−91	−23
Cerebellum II	**L**	**4.08**	**−27**	**−67**	**−40**						
						Cerebellum II	R	4.73	39	−68	−48
						Cerebellum II	R	3.64	21	−81	−38
						Cerebellum IV–V	L	7.31	−18	−24	−30
Calcarine	R	3.32	8	−86	3						
Middle temporal	**R**	**11.02**	**66**	**−32**	**−13**	Middle temporal	R	5.92	64	−11	−24
Middle temporal	**L**	**2.27**	**−59**	**−48**	**−3**	Middle temporal	L	6.43	−61	−51	−5
Inferior temporal	R	8.85	54	−5	−30						
Inferior temporal	**L**	**3.06**	**−54**	**−13**	**−28**	Inferior temporal	L	4.11	−54	−15	−26
Angular gyrus	**L**	**7.63**	**−48**	**−61**	**29**	Angular	L	7.70	−44	−64	28
						Angular	L	5.85	−42	−62	56
Angular gyrus	**R**	**4.18**	**55**	**−57**	**39**	Angular	R	8.48	53	−63	27
Superior frontal	**L**	**3.57**	**−11**	**60**	**7**	Superior frontal	L	4.57	−18	30	50
Superior frontal	**L**	**3.79**	**−14**	**23**	**63**	Superior frontal	L	2.30	−12	54	31
Superior frontal	**R**	**2.48**	**25**	**61**	**13**	Superior frontal	R	3.40	19	60	18
Superior medial frontal	**R**	**6.97**	**0**	**44**	**33**	Superior medial frontal	R	4.11	12	43	46
Middle frontal	**R**	**5.38**	**41**	**16**	**52**	Middle frontal	R	3.47	46	17	49
Middle frontal	**L**	**4.71**	**−41**	**15**	**47**	Middle frontal	L	4.38	−43	12	47
Middle orbito-frontal	R	2.04	5	34	−12						
						Middle orbito-frontal	L	4.79	−1	50	−4
Inferior orbito-frontal	R	9.51	45	41	−13						
						SMA	R	3.24	2	12	74
Middle Cingulate	**R**	**3.82**	**2**	**−21**	**35**	Middle Cingulate	R	7.62	1	−31	37
						Parahippocampal	R	2.54	28	−18	−24
						Thalamus	L	3.52	−6	−13	2
Precuneus	**R**	**4.96**	**3**	**−63**	**38**	Precuneus	R	12.92	0	−66	34
Lingual	**L**	**4.96**	**−3**	**−44**	**3**	Lingual	L	5.03	−1	−50	5

[a] Regions in bold were the regions of interest used in the present analysis.

i.e., the integration within the DMN can be decomposed into the sum of the integration within the ANT and POST subnetworks, and the integration between both subnetworks. These four integration values were calculated for each participant.

2.9. Statistical analysis

A one-way analysis of variance (ANOVA) was applied to assess group effects, using integration values as the dependent variable and the group as the independent variable. To test a potential time effect, we used a *t* test for dependent samples. For the participants with aphasia, Pearson's correlations between the DMN integration values and the degree of improvement were calculated. Correlations between DMN integration values and the number of training sessions received were calculated for the two groups: controls and participants with aphasia.

3. Results

3.1. Behavioural results

As reported in Marcotte et al. (2012), all participants suffering from aphasia benefited from SFA therapy, with a mean improvement of 80% ± 13.3. Fig. 2 provides a single-case longitudinal perspective of behavioral changes along therapy with SFA. All participants with aphasia showed some degree of generalization of SFA effects to untrained material where the mean improvement with untrained stimuli was 21.3% ± 5.8. Still, the difference in improvement with trained and untrained items was statistically significant ($t = 13.98$, $P < 0.001$). With regards to the duration of therapy, these gains were obtained within an average number of 12.7 ± 4.2 sessions.

For the healthy elderly control group, the mean accuracy score in the French naming task was 100% ± 0 during both fMRI sessions. Thus, as expected there was no significant difference in naming accuracy in French. Conversely, the mean accuracy score in Spanish was 32.8% ± 11.6 at the early learning phase, and 96.5% ± 2.8. At the consolidation phase, response times in French were 1.20 s ± 0.21 at time 1, 1.15 s ± 0 24 at time 2, thus showing no significant difference in the response time in French ($t = 1.48$, $P = 0.173$) across time measures. Conversely, in Spanish, there was a main effect of learning phase ($t = 2.78$, $P = 0.022$), showing faster response times at the consolidation phase (mean = 1.37 s ± 0.33) than at the early learning phase (mean = 1.92 s ± 0.52).

For the participants with aphasia, the mean accuracy score in the naming task was 34.6% ± 5.4 during the first fMRI session. After therapy, the mean accuracy score was 60.8% ± 7.8. Thus, there was a significant difference in naming ($W(8) = 2.670$, $P = 0.008$). Regarding the response time before therapy, correct responses were given 2.07 s ± 0.47 after the presentation of the picture. After therapy, the mean response time was of 1.99 s ± 0.51. Thus, there was no significant difference in the response time ($W(9) = -1.274$, $P = 0.203$).

3.2. Imaging results

3.2.1. Spatial maps

Connectivity analyses were conducted on a block design mode, for both groups. This implies that for the individuals with aphasia, the reported results are based on both correct and incorrect responses. Thus, this approach provides a global picture of the network and its status before, and after therapy. The brain areas contained in the DMN for the control and aphasia groups—before and after training—are shown in Fig. 3. Multidimensional scaling was not suitable to represent the distance matrix between both

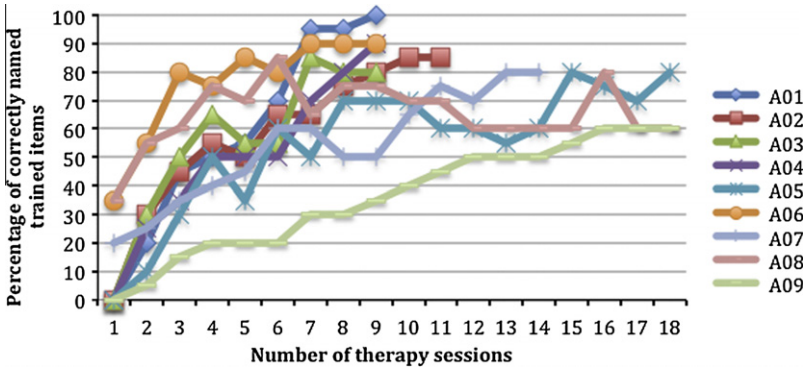

Fig. 2. Single-case longitudinal perspective of behavioral changes along therapy with semantic feature analysis.

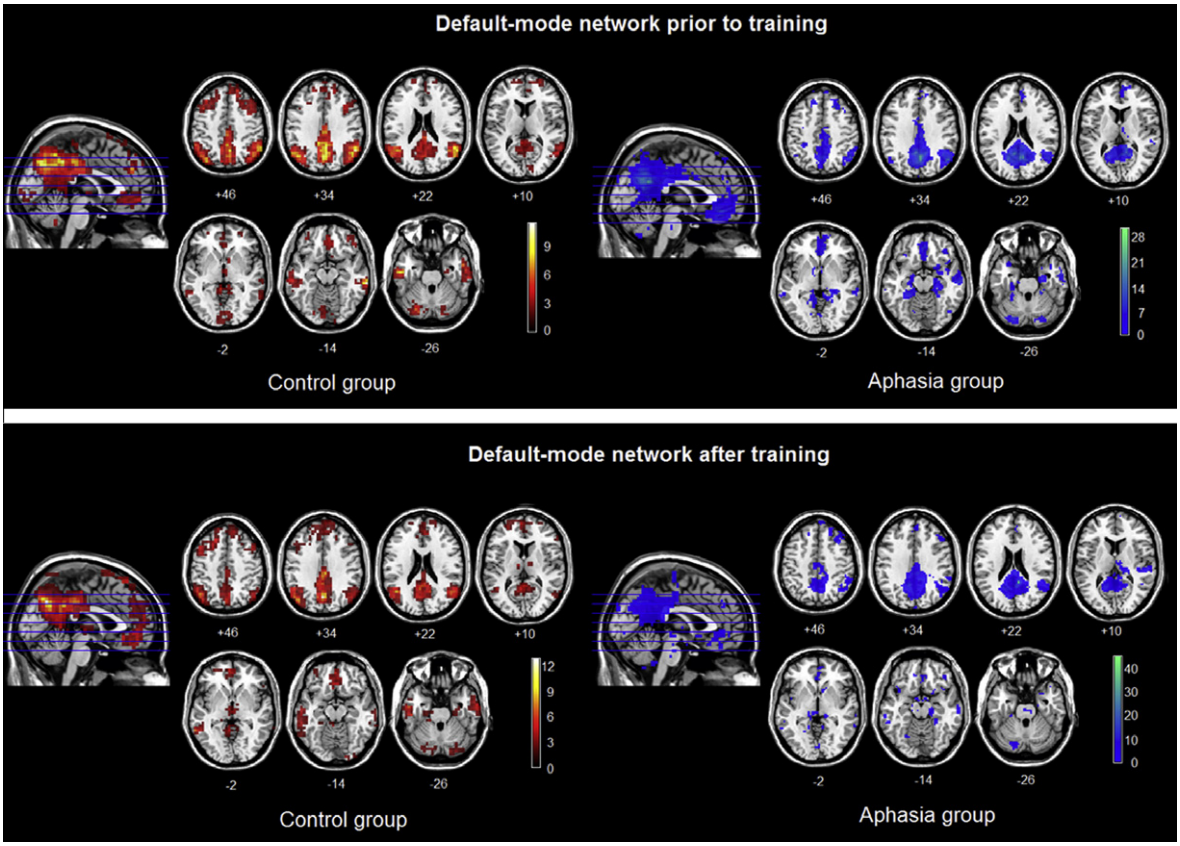

Fig. 3. Default-mode network identified in healthy elderly controls and patients with aphasia—prior to (top) and after (bottom) language training. Threshold results ($P < 0.005$) are uncorrected and superimposed on an anatomical template in the functional magnetic resonance imaging (fMRI) standard space. Images are shown in neurological convention (i.e. the left side corresponds to the left side of the brain).

groups and time points, since the distances were too large between both groups.

Within the group-representative maps, maps exhibiting a spatial organization corresponding to the DMN were identified. These maps were identified for each run, and their representativity and unicity were both 1 for the controls. For the aphasic participants, representativity of the DMN was 0.78, but unicity was 1.

T1–T2 DMN patterns were more stable in the control group than in the patient group. In the control group, the DMN contained 20 areas prior to training and 23 areas after training, with 16 common areas in both T1 and T2 measures, which were identified as regions of interest. These included the superior and middle frontal gyrus, the middle temporal cortex and angular gyrus bilaterally, the left inferior temporal cortex and the right middle cingulate, and the right cerebellum (Table 2). In the patient group, of the 24 areas in the DMN at T1 and the 23 areas in the DMN at T2, 9 were common at both times. The common areas included the middle temporal cortex and cingulate bilaterally, the left superior frontal gyrus, the right superior medial frontal cortex, and the left cerebellum (Table 3). Four participants had lesions in areas included in the canonical DMN, but no more than two patients had a lesion in the same area; thus 75% of the DMN components were preserved in our sample.

To examine functional integration changes in the DMN, only the common areas identified in both fMRI sessions in the healthy control group were used. Since this is the first study to examine the DMN in aphasia, and in line with previous functional connectivity studies with clinical populations, the focus was put on the

Table 3
Significant connectivity peaks in patients with aphasia before and after lexical training.

Aphasia group: Default-mode network prior to therapy						Aphasia group: Default-mode network after therapy					
Peak label	Peak MNI coordinates					Peak label	Peak MNI coordinates				
		Peak *t*-score	*x*	*y*	*z*			Peak *t*-score	*x*	*y*	*z*
Cerebellum II	L	7.07	−29	−80	−34	Cerebellum II	L	4.31	−30	−79	−36
Cerebellum IX	L	4.09	−9	−50	−43						
Cerebellum IV–V	R	5.88	22	−35	−25						
Cerebellum I	R	4.33	23	−79	−27						
						Cerebellum IX	R	3.79	9	−49	−46
						Cerebellum VI	L	2.72	−26	−32	−29
Calcarine	L	2.16	−23	−58	13	Calcarine	L	3.57	−20	−56	12
Superior temporal	R	5.96	25	4	−21						
						Superior temporal pole	L	4.87	−47	8	−8
Middle temporal	R	7.12	62	−16	−65	Middle temporal	R	5.38	64	−20	−12
Middle temporal	L	2.44	−62	−38	−4	Middle temporal	L	5.06	−61	−28	−13
						Middle Temporal pole	R	2.08	41	17	−35
						Middle temporal	R	4.62	56	−56	23
Inferior temporal	L	6.17	−50	9	−35						
Fusiform	L	3.05	−26	−32	−20						
Angular gyrus	R	12.25	51	−63	31						
Angular gyrus	L	2.21	−50	−66	32						
Superior frontal	L	4.51	−17	34	57	Superior frontal	L	2.43	−32	−38	71
Superior frontal	R	4.20	25	29	48						
Superior medial frontal	R	2.90	7	57	11	Superior medial frontal	R	3.45	9	54	46
						Superior medial frontal	R	4.27	42	29	41
						Middle frontal	R	2.50	25	20	63
Inferior orbito-frontal	R	2.89	38	36	−14						
						Rolandic operculum	R	3.01	44	−28	14
						SMA	L	2.63	0	−20	71
Rectus	R	7.37	1	41	−13	Rectus	R	2.57	2	39	−19
						Superior parietal	R	3.15	39	−62	47
Inferior parietal	L	2.67	−32	−39	47						
						Postcentral	R		9	−45	23
Precuneus	R	29.07	4	−62	31						
Precuneus	R	2.99	5	−51	69						
						Cuneus	L	7.49	−5	−75	29
Lingual gyrus	R	5.40	13	−45	5						
Cingulate	R	6.57	3	−21	37	Cingulate	R	45.75	8	−49	23
Cingulate	L	3.02	−2	7	31	Cingulate	L	3.69	−4	−22	10
Pallidum	L	2.18	−12	2	−5						
						Calcarine	R	4.41	15	−88	−8
						Caudate	R	3.37	11	14	−6

canonical DMN identified in healthy controls, which was consistent across measures and in line with previous literature. Defining the DMN from the data obtained in stroke patients seems risky at this point since the concept of the DMN is still evolving. Still, we wanted to report the changes observed after therapy in the data-emergent DMN, which we did in Table 3. Then, the DMN was subdivided into the anterior and posterior subnetworks in accordance with the disconnection hypothesis. The anterior subnetwork was composed of the superior and middle frontal gyrus bilaterally as well as the left superior medial frontal cortex. The regions of interest of the posterior subnetwork included the middle temporal cortex and angular gyrus bilaterally, the left inferior temporal cortex and the right middle cingulate and the right cerebellum, and the left inferior temporal cortex and the right middle cingulate.

3.2.2. Hierarchical integration

Hierarchical integration of the levels of the DMN was computed for anterior, posterior and between-network integration, for both runs. Statistical tests between pairs of integration values at T1 and T2 were computed for each group and across groups.

3.2.2.1. Default-mode network integration (I_{DMN}). A within-group *t* test for dependent samples showed no significant differences between T1 and T2 I_{DMN} for the control group ($P = 0.464$) or for the patient group ($P = 0.545$). A between-group ANOVA with T1 measures showed that DMN integration values were significantly higher in the control group than in the patient group ($F[2,17] = 5.687$, $P = 0.029$), whereas there were no significant differences between integration values across groups at T2 ($F[2,17] = 0.717$, $P = 0.409$). The mean integration values and their standard deviations (SDs) are shown in Fig. 4.

3.2.2.2. Anterior subnetwork integration (I_{ANT}). A within-group *t* test for dependant samples showed no significant difference between T1 and T2 I_{ANT}, with the control group ($P = 0.392$) or the patient group ($P = 0.880$). Conversely, a between-group ANOVA showed that anterior subnetwork integration values (i.e. frontal areas) showed no significant difference between the control group and the patient group both at T1 ($F[2,17] = 4.039$, $P = 0.061$) and at T2 ($F[2,17] = 1.04$, $P = 0.322$) (see Fig. 4 for the mean integration values and SDs).

3.2.2.3. Posterior subnetwork integration (I_{POST}). A within-group *t* test for dependent samples showed no significant difference between T1 and T2 I_{POST} in the control group ($P = 0.392$). Conversely, I_{POST} values were significantly higher after therapy in the patient group ($P = 0.046$). Posterior subnetwork integration values (i.e. posterior areas) were significantly higher in the control group than in the patient group, both at T1 ($F[2,17] = 38.101$, $P < 0.001$) and at T2 ($F(2,17) = 10.750$, $P = 0.005$) (see Fig. 4 for the mean integration values and SDs).

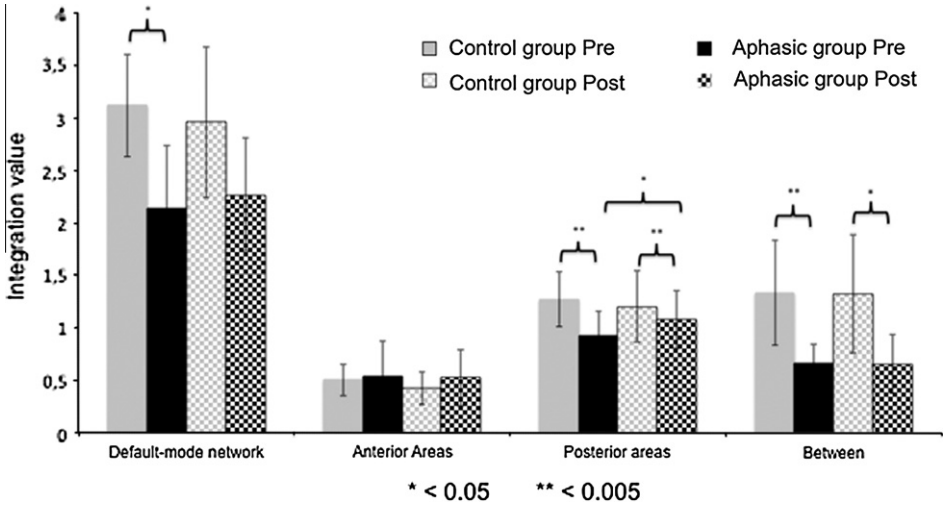

Fig. 4. Default-mode network integration in the whole network, within the anterior areas, within the posterior areas, and between the anterior and posterior areas – for control subjects and patients with aphasia, before and after language training.

3.2.2.4. Between subnetworks integration ($I_{BETWEEN}$). A within-group *t* test for dependent samples showed no significant difference between T1 and T2 I_{BET}, both with the control group ($P = 0.963$) and the patient group ($P = 0.866$). A between-group ANOVA showed I_{BET} values (i.e. between anterior and posterior subnetworks) were significantly higher in the control group than in the patient group at T1 ($F[2,17] = 11.893$, $P < 0.003$). At T2, I_{BET} values were still significantly higher in the control group than in the patient group ($F[2,17] = 9.896$, $P = 0{,}006$) (see Fig. 4 for the mean integration values and SDs).

3.2.3. Correlations between DMN and post-therapy improvement in participants with aphasia

Correlations with improvement were calculated with participants with aphasia only, as the control group performed at 100% at both times. None of the correlations between the degree of language improvement and integration measures both at T1 and T2 reached significance at a confidence interval of 95%. However, a trend seems to emerge between language improvement and DMN, anterior subnetwork and between-network integration measures at T1 only (Pearson correlation: $r = 0.596$, $P = 0.09$; $r = 0.642$, $P = 0.062$; $r = 0.618$; $P = 0.076$ respectively) (see Fig. 5 for the representation of the DMN integration correlations at T1 and T2 and improvement following therapy values and SDs).

None of the correlations between the number of therapy hours received by participants with aphasia and DNM integration values obtained before and after therapy reached significance (I_{DMN} T1: $r = -0.298$, $P = 0.436$, and at T2: $r = 0.224$, $P = 0.563$). This was also the case with the control group (I_{DMN} at T1: $r = 0.179$, $P = 0.620$, and at T2: $r = 0.092$, $P = 0.800$). Moreover, no significant correlations between the number of training sessions and I_{ANT}, I_{POST} and I_{BET} were observed across either group at either time.

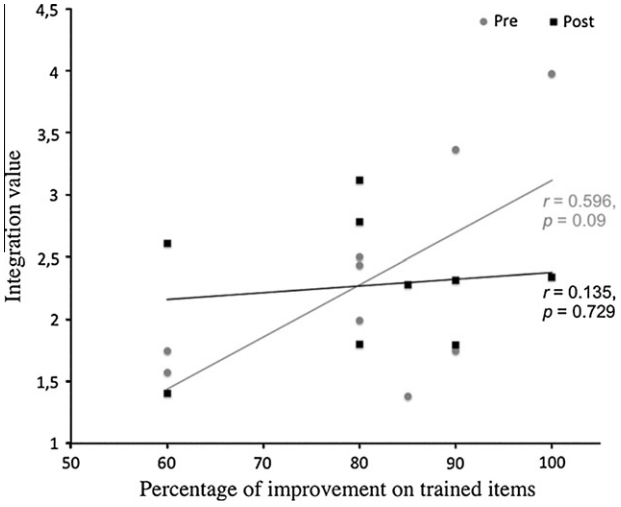

Fig. 5. Correlations of default-mode network integration at T1 and T2 and improvement following therapy.

4. Discussion

We examined the DMN functional connectivity in participants with aphasia receiving intensive language therapy with SFA. The DMN, as identified in a group of control participants, was also detected in participants with aphasia, both before and after SFA therapy. Three important findings were made. First, to our knowledge, this is the first time that the DMN has been identified in participants with aphasia, and the first time that therapy-induced neuroplasticity in the DMN has been described in post-stroke aphasia. Second, the areas contained in the DMN were very different between T1 and T2 in the participants with aphasia, whereas they remained relatively stable in the control subjects. Third, DMN modulation was observed in the posterior areas after training in participants suffering from aphasia only. These results demonstrate that focal brain lesions not only have local damage but also induce persistent and more complex modifications on large-scale networks (Nomura et al., 2010; Warren et al., 2009) that are not primarily known for their role in language processing.

Using hierarchical integration, an anterior–posterior disconnection was observed in participants with aphasia, as compared to healthy controls, in line with evidence from healthy elderly with functional deficits (Davis et al., 2009; Madden et al., 2009), and Alzheimer's disease (Grady et al., 2001). However, in the present study, intensive SFA therapy did not significantly increase integration between anterior and posterior subnetworks in the participants with aphasia. Increased integration was revealed in the posterior subnetwork following intensive SFA therapy. Within this subnetwork, the precuneus is a prominent node, systematically identified in the DMN (Mevel et al., 2010). The precuneus

has been recently reported as being modulated following improvement in participants with chronic aphasia (e.g. Fridriksson, 2010; Fridriksson et al., 2007) and with decreased activation during a naming task in a group of patients with frontotemporal lobar degeneration (Frings et al., 2010). The posterior subnetwork is also composed of temporal areas; bilateral temporal lobe activations in object naming have been reported in non-brain-damaged subjects (Warburton, Price, Swinburn, & Wise, 1999), and left middle temporal and the superior temporal ones have been associated with lexical selection (Indefrey & Levelt, 2004). In fact, activations in the middle temporal lobe reported within the DMN in both groups are in line with findings from previous studies (Greicius & Menon, 2004; Christoff et al., 2004), and thus we consider these areas as part of the DMN. However, it is possible that some of the activity reported is language related activity given that some of the areas within the posterior part of the DMN (i.e. the left superior temporal cortex and the angular gyrus) are language eloquent cortex. In the present case, greater integration in the brain areas involved in semantic encoding, lexical selection and can be related to increased boosting of distinguishing semantic features with SFA (Boyle, 2004). As well, considering the behavioral improvement observed, these results suggest that changes in the DMN reflect brain reorganization following therapy. Still, the integration values in the posterior subnetwork were higher in the healthy control group than in participants with aphasia after therapy. These results support a recent proposition by Zhang et al. (2010) suggesting that functional connectivity abnormalities may reflect cognitive impairments of corresponding DMN regions. By segmenting the DMN, significant changes were identified following therapy, which the study of the whole DMN would have missed. The present result also supports our hypothesis that language improvement following therapy would be associated with greater functional connectivity between the different regions of the canonical DMN.

Regarding the DMN as a whole, the correlation between DMN integration before therapy and positive outcomes following therapy did not reach significance; we speculate that this correlation would have reached significance with a larger sample, and highlight the potential of a prognostic value of pre-therapy DMN status in aphasia. DMN functional connectivity might thus become an efficient, neurobiologically-based interventional and prognostic tool, to identify an optimal window of opportunity for effective intervention and positive outcomes. The DMN prognosis value was observed in comatose patients (Vanhaudenhuyse et al., 2010) and in multiple sclerosis patients (Rocca et al., 2010). However, a similar trend was not observed between improved DMN integration following therapy and post-therapy language improvement. This suggests that after training, the task required less cognitive control demands for participants with aphasia and that the task is more automatic.

Integration within the anterior subnetwork was not significantly different between healthy controls and participants with aphasia, as opposed to multiple sclerosis patients (Bonavita et al., 2011; Rocca et al., 2010). Successful therapy outcomes were not significantly correlated with pre-therapy functional integration, but a trend also seemed to emerge from the data between the anterior subnetwork integration and improvement following therapy. The anterior subnetwork comprised the right medial frontal lobe as well as the superior and middle frontal lobe bilaterally, areas that have been associated with attention deficits in patients with aphasia or right-hemisphere damage (Glosser & Goodglass, 1990). However, we did not include any measure of attention in this study. One possible explanation for this is that following a stroke, patients with aphasia require more cognitive control in order to improve. The role of executive functioning in healthy (Ansaldo, Marcotte, Scherer, & Raboyeau, 2008) and brain-damaged bilingual populations (Abutalebi, Rosa, Tettamanti, Green, & Cappa, 2009) is receiving increasing interest. Moreover, the degree of cognitive control required for a specific task could modulate connectivity in the DMN (McKiernan et al., 2003; van de Ven et al., 2009). Thus, patients for whom the task is less difficult require less cognitive control to sustain performance, and thus improve the most.

The evidence reported here reinforces the role of large-scale networks in cognitive processes, and argues for the validity of sICA in the understanding of recovery mechanisms following brain injury (Honey & Sporns, 2008). Considering the complexity of language processing, which includes semantic, lexical and phonological levels, motor programming, as well as access to visual and memory representations in oral naming, a functional connectivity approach that can detect network interactions seems particularly suitable to characterize post-stroke recovery (van de Ven et al., 2009). Another advantage of sICA is related to its data-driven approach. Unlike structural equation modeling, sICA does not require identification of seed areas, which is a large advantage when the research literature does not provide sufficient information to justify the use of specific brain networks or areas to study the effect of a disease (Rowe, 2010), as in aphasia. In addition, sICA incorporates a measure of hierarchical integration that summarizes all the correlation coefficients in a single value and allows the calculation of between-network integration (Marrelec et al., 2008), a measure sensitive to behavior-induced dynamic changes (Coynel et al., 2010).

Based on the present data, we recognize that no significant relationship between the integration values and therapy improvements was found. We also acknowledge that both hits and errors are included in the analysis, but the integration changes obtained were observed concurrently with behavioral improvement induced by SFA, in a group of chronic and stable participants with aphasia. Within this frame, we believe that the changes observed in the DMN were observed in the context of a successful outcome following therapy. Another possibility is that part of this effect is not therapy specific but relates to practice, as already reported in previous studies on aphasia therapy (Cardebat et al., 2003). However, given that brain activation patterns associated with object naming appear to be stable across repeated fMRI scans in chronic aphasia (Fridriksson, Morrow-Odom, Moser, Fridriksson, & Baylis, 2006), and given that in the present study this is not the case, the possibility that changes observed across sessions reflect a therapy effect is likely. Still, further studies could explore the impact of SFA on more participants suffering from aphasia to support our hypothesis.

Using this approach, we were able to identify the DMN at both times of measurement and in both groups. The present results suggest that functional connectivity may represent an interesting alternative to standard fMRI protocols to assess therapy effects in participants with aphasia. Moreover, given their lower cost and time needs as compared to standard fMRI protocols, further research on functional connectivity may highlight important information regarding aphasia and its recovery in general. Studies of the DMN in clinical populations have usually compared it with rest conditions (McKiernan et al., 2003; Raichle et al., 2001). However, there is one main methodological weakness in the present study. DMN has not been compared with a rest condition, but rather with itself. In the original design of these two groups, we did not include a rest condition, but rather used a control condition that matched the experimental condition as much as possible in order to get meaningful results. Thus, in the near future, we should directly compare rest and naming conditions in order to see if the changes that have been identified in the DMN can also be found when the behavior is measured outside the scanner, as observed by Carter et al. (2010). We should also recruit more participants to look more

closely at the possible prognosis value of the DMN in chronic aphasia.

Moreover, we chose to focus on the canonical DMN, so as to be able to compare a single network across participants with aphasia and healthy controls. A recent connectivity study showed that a brain lesion does not only affect the damaged area but the interconnected areas as well (Nomura et al., 2010) and thus we can hypothesize that there was an impact of brain damage in our sample as well. However, in line with Nomura et al. (2010), to be able to specifically appreciate a lesion effect, a much larger sample would be necessary. The evidence reported here suggests that language therapy can have a positive impact in improving information flow within the canonical DMN, despite permanent damage to some of its components. Finally, another possible drawback of this study was caused by an upgrade between the two studies. The scanning parameters have been changed after the upgrade, which could also influence our results. However, even if the parameters have been changed, we are pretty confident that our results are reliable. A recent study reported a very high reproducibility in networks detected using ICA in a large database (Functional connectome: http://www.nitrc.org/projects/fcon_1000) for sequences that were relatively different (Biswal et al., 2010).

5. Conclusion

The present results showed a decreased connectivity in the posterior subnetwork and in a group of participants suffering from chronic aphasia as compared to healthy elderly controls. Moreover, behavioral improvement following a language therapy was identified concurrently with changes in the posterior subnetwork of the DMN.

Author Disclosure Statement

No competing financial interests exist.

Acknowledgments

This study was supported by a Canadian Institute in Health Research Doctoral grant to K.M. and a Fonds de recherche en santé du Québec grant and a CAREC grant to A.I.A. The authors would like to thank the participants and their families for their time and their engagement in this project.

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