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Interaction between language and analogical reasoning from

the brain imaging perspective

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Chapter I

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Introduction

Analogy (from Greek "*ανα-λογος*", "related to") is the cognitive process of transferring information from a particular subject (the analogue or source) to another particular subject (the target), deriving the relationship between a group of items and then applying that relationship to help the reasoning about a different group of items. Traditionally, an analogy is represented as a four term problem: "A:B as C:D". The solution requires the ability to retrieve information-concepts from semantic memory, the ability to form and manipulate mental representations of relations between objects and events, and to compare the resulting prepositions between pairs (Bunge, Wendelken, Badre, & Wagner, 2005). Analogical reasoning is considered a core component of intelligence and cognition (Gentner, 2003): the relational thinking allows us to concatenate previous/different experiences/concepts and arrive at a new conclusion, as well as to generalize experience from particulars. The analogical thinking is the ground/basis of metaphors and gives us the possibility to use concrete concepts/experience/relations for discussing and explaining new abstract ideas

Functional neuroimaging studies that examined the neural basis of analogical reasoning documented a clear left hemisphere involvement: relational thinking in general elicits strong activity in a left-lateralized group of brain regions among which the core area appears to be the left prefrontal cortex (Boroojerdi et al., 2001; Bunge, et

al., 2005; Cho et al.; Christoff et al., 2001; Kroger et al., 2002; Monti, Parsons, & Osherson, 2009). As a consequence, particular interest has been devoted to the functional organization within the prefrontal cortex to investigate if/how different sub-regions subserve different components of the reasoning process (Bunge, et al., 2005; Cho, et al.; Hampshire, Thompson, Duncan, & Owen, 2011; Volle, Gilbert, Benoit, & Burgess).

In addition to the prefrontal cortex, brain areas traditionally related to verbal language may be involved to a different extent and grading in reasoning (Bunge, et al., 2005; Christoff, et al., 2001; Green, Kraemer, Fugelsang, Gray, & Dunbar, 2010; Hampshire, et al., 2011; Luo et al., 2003; Prabhakaran, Smith, Desmond, Glover, & Gabrieli, 1997; Wharton et al., 2000; Whitney, Grossman, & Kircher, 2009). On the same track, clinical data suggest that the integrity of the language-dominant hemisphere is necessary to solve analogical tasks (Baldo, Bunge, Wilson, & Dronkers, 2010; Baldo et al., 2005; Langdon & Warrington, 2000). Langdon and Warrington documented that patients with left hemisphere lesions were impaired on both verbal and visuo-spatial tasks (Langdon & Warrington, 2000); Baldo and Colleagues, studying left-hemisphere stroke patients, suggest a correlation between non-verbal relational thinking and a lesion of core language regions such as the superior and middle temporal gyrus (Baldo, et al., 2010; Baldo, et al., 2005). On the other hand, studies with Alzheimer's disease patients suggest that the left prefrontal areas critical for relational reasoning are those subserving working memory and executive functions, traditionally not considered core areas for language processing (Waltz et al., 2004; Waltz et al., 1999).

These observations agree with many behavioral evidences of the involvement of language in reasoning (Baldo, et al., 2005; Carruthers & Bermùdez, 2006; Hermer-Vazquez, Spelke, & Katsnelson, 1999). Gentner (2003) proposed a more general theoretical framework for reasoning within which language provides an internal cognitive tool which fosters high order relational concepts throughout the possibility to use linguistically shaped relations. The ability to use words that refer to relations (such as "cause", "inhibit", "source", "advantage", etc), that Gentner calls "relational language", help us to manipulate concepts, relations, and abstract entities. Thus, in Gentner's position, verbal language provides a symbolic system which serves to develop and learn relational concepts and provides cognitive stability to them. In this view, the development/acquisition of language, and in particular the relational language, during childhood contributes to the development of analogy and cognition because language provides the control over mental processes (Vygotsky, 1962). Learning specific relational terms provides representational resources that augment cognitive processes and the possibility of abstraction and generalization (Gentner, 2003; Gentner & Christie, 2010).

Despite the evidences about the strong link between language and thinking, the neural substrate of verbal language comprise a widespread network of mostly left lateralized brain areas each subserving different aspects of verbal language (Price, 2000, 2010). It is unclear if all components of verbal language are needed, support or influence the reasoning itself.

Some behavioral studies suggest a role of covert verbalization during flexible thinking (Baldo, et al., 2005; Carruthers & Bermùdez, 2006; Hermer-Vazquez, et al.,

1999). On the other hand, functional neuroimaging studies demonstrated that the classical Wernicke-Broca circuit, which subserves overt and covet verbalization by means of lexical and phonological processing, may be not necessary to perform reasoning unless verbal language is needed for the decoding of the terms (Monti, et al., 2009). Interestingly, there area data in the literature which suggest that the access to the conceptual knowledge, that is the mandatory step for analogical reasoning, may differ depending on the stimulation modality. For example, Saffran et al. (2003) demonstrated that pictures and words representing semantic concept evoked significantly different words associations. Caramazza (1990) suggested that visually presented objects`, through their perceptual features`, may have a more direct access to semantic knowledge. Thus, even without entering the question about how conceptual knowledge is organized in the brain, it is clear that its retrieval and manipulation may be influenced by the stimulation modality. It is then possible also to argue that the reasoning may be affected by the stimulus format. While it is known that other factors, such as the number of visuo-spatial relationships (Christoff, et al., 2001), the relational complexity (Kroger, et al., 2002), and the associative strength (Bunge, et al., 2005), strongly influence the activity of the prefrontal cortex during reasoning, to our knowledge, only one study investigated the modulation induced by the stimulation context on reasoning using abstract and meaningful pictures. Even in that case the analysis has been "limited" to the prefrontal cortex subregions (Krawczyk, Michelle McClelland, & Donovan, 2011).

When I originally planned the research activity for this thesis, the principal aim of my work was to study the higher cognitive functions, in particular the analogical reasoning, in a young population of dyslexics in order to understand if the reading disorder may influence the reasoning in relation to the language load requested by the stimulus format. In fact, independently from the theoretical approaches to dyslexia and the cognitive domain explored, up to now the data available in the literature deal mainly with the nature of the deficit associated with developmental dyslexia. But evidences also suggest that developmental dyslexics may have a talent for activities related to the non-verbal domain including complex reasoning. The question I wanted to investigate was if this observation could be linked to a particular neural brain organization both at the structural and functional level. For this reason I developed an fMRI paradigm to investigate brain activity during analogical reasoning performed either with words or pictures. The hypothesis was that, if a particular talent is present in dyslexics, they may have shown significant brain reorganization compared to normal readers, especially with pictures which allow but do not require a mandatory use of language.

As a first step the fMRI paradigm was applied to study a sample of normal adults. This study allowed to verify how much reasoning relies on verbal language. In fact, despite the increasing interest about the neural substrates of reasoning, at present no fMRI study systematically investigates the contribution of stimulus format/context on reasoning network, within the same study and with the same paradigm. Thus, the

results of this first study will focus on how different verbal context, nameable pictures versus words, may influence brain activity related to analogical reasoning.

In a second study the same paradigm was applied to investigate brain activity during analogical reasoning in young normal readers and young dyslexics in order to tackle the main question that I wanted to investigate.

Finally, considering the results of the first two fMRI studies, a new question arose about the contribution of language and semantic system to reasoning. Thus, a new fMRI design was implemented where analogical reasoning had to be performed either on meaningful or on abstract geometrical pictures. Results form this last study provided new information about the relation between language and analogical reasoning that could be derived form the observation of the brain activity elicited by the two contexts.

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Chapter II

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Brain activity during analogical reasoning within different verbal contexts: words *vs.* nameable pictures

The aim of this study was to explore how brain areas responsive to analogical reasoning are modulated by the modality of access to semantic information, using words and nameable pictures to present the terms of the analogy. We assumed that words require a mandatory phonological and lexical elaboration in order to access the underlying semantic information. This also may trigger a more verbal strategy to manipulate the information in order to perform the reasoning. In this respect one may expect that covert verbalization or inner speech may be always present in a word context. Instead, when pictures are presented, despite lexical-phonological processing is possible, and may be somewhat automatically triggered in order to name the picture, the use of covert verbalization is not mandatory since pictures may have a more direct access to the semantic system and convey enough information for the reasoning even without any lexical-phonological support.

We implemented a block fMRI design where analogical reasoning task had to be performed in word and picture context. We provided a limited time interval during which the response could be given. Then, we focused the attention on those brain areas

indicated by the literature to be critical for reasoning, verbal language and conceptual-semantic competences. In the present study the term "core language areas" will be used referring to the standard thesis about the localization of language which assert that human linguistic components are embodied by structures close to the left sylvian fissure - i.e. the classical Wernicke-Broca circuit (Bookheimer, 2002; Monti, et al., 2009).

On the basis of the literature we expected that core areas for reasoning in prefrontal cortex as well as areas known to be part of semantic system should not be modulated by the context of reasoning. Differently, the behavior of core language areas can be informative respect to the influence of context in analogical reasoning. We assumed that when reasoning is performed on words the involvement of the lexical-phonological system is mandatory to access the meaning, but its involvement is not obvious in a picture context. If the hypothesis of a "privileged access" suggested by Caramazza et al. (1990) is true, reasoning within a picture context may not engage the core language regions, especially in the case of a short time available for the response. Differently, in case a covert verbalization strategy is needed for reasoning despite the context on which it is performed, we should expect an involvement of verbal language areas also within a picture context.

Material and Methods

Subjects

15 right-handed subjects were recruited for this study (7 males and 8 females, mean age 27 years, range 22-42). All participants were Italian native speakers with no history of neurological or psychiatric disorders. Handedness was assessed using the Edinburgh Inventory (Oldfield, 1971). The study was approved by the Ethics Committee of the University of Trento and all participants signed an informed consent form.

Stimuli

The stimuli of picture context were drawn and modified from the Non Verbal Intelligence Test (Wiederholt, 2004). We prepared 24 stimuli for each task: the analogical reasoning (AnR) and the semantic judgment (Sem). In the Picture-AnR task, each stimulus was composed by two pairs of grey scale pictures; in the Picture-Sem task each stimulus was composed by a triplet of grey scale pictures. In 16 of the Picture-AnR stimuli, the two picture pairs had the same type of analogical relationship (True Items) while in the remaining 8 stimuli the type of relationship was different (False Items). Similarly, in 16 Picture-Sem stimuli the three pictures belonged to the same category (True items) while 8 did not (False items). Figure 1a and 1b shows an example of the stimuli used.

The stimuli for word context were prepared on the basis of the picture context task, with 24 stimuli for each task. In Word-AnR each stimulus was composed by two

pairs of words; in Word-Sem each stimulus was composed by a triplet of words. In 16 of the Word-AnR stimuli, the two words pairs had the same type of analogical relationship (True Items) while in 8 stimuli the type of relationship was different (False Items). Similarly, in 16 Word-Sem stimuli the three words belonged to the same semantic category (True items) while 8 did not (False Items).

The words were controlled for frequency based on the corpus COLFIS (http://alphalinguistica.sns.it/BancheDati.htm) and no significant differences were found between stimuli used for the AnR and the Sem task. Figure 2.1 shows an example of the stimuli used.

The words and picture stimuli used in both tasks were matched for two main factors: the ratio of living/non-living items and the semantic distance. Semantic distance was computed based on Likert ratings (1 = low semantic distance, 7 = high semantic distance) given by 20 subjects who did not participate to the fMRI experiment. Each pair of items used in the AnR task and each triplets used in the Sem task was judged individually. A two-tail t-test for unpaired samples did not reveal any significant difference in semantic distance between picture and word items within each task (Picture-AnR: mean 2.97, sd 0.59; Word-AnR: mean 2.86, sd 0.52, p=0.48 n.s.; Picture-Sem: 3.37, sd 1.14; Word-Sem: mean 3.17, sd 0.65, p=0.46, n.s.).

Figure 2.1 Examples of the stimuli used
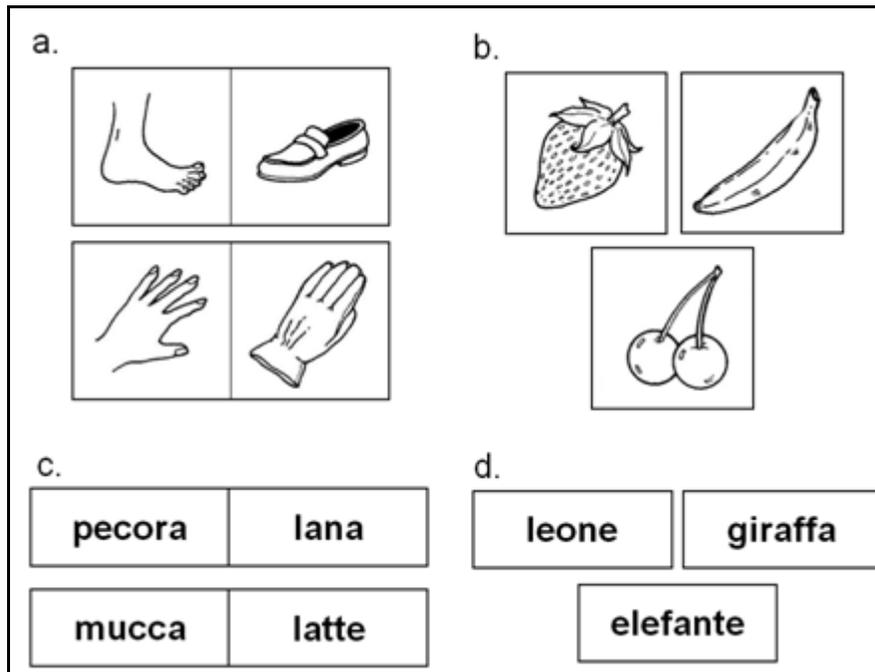
(a) Picture analogical reasoning; (b) Picture semantic judgment; (c) Word analogical reasoning; (d) Word semantic judgment. Transl: ("pecora"=sheep; "lana"=wool; "mucca"=cow; "latte"=milk; "leone"=lion; "giraffa"=giraffe; "elefante"=elephant).

Tasks, fMRI design and procedure

The presentation of the stimuli was performed using a block fMRI design with one run for each context (Word and Picture). Each run contained 12 blocks, six for each task (AnR and Sem) presented alternately. Each block contained four stimuli and it was preceded by specific instructions for task and context lasting 2 s. On AnR task, participants viewed the two pairs of pictures or words displayed simultaneously on the screen and they had to indicate whether the analogical relationship between the two pairs of items was or was not the same. On the Sem task, participants viewed the three pictures or words displayed simultaneously on the screen and they had to

indicate whether the three items belonged to the same semantic category. In both tasks, participants were required to make a yes/no response only during the presentation by pressing one of two buttons of a response pad with their right hand.

The minimum and maximum stimulus durations were 500 and 5500 ms respectively. For response times faster than 500 ms, the stimulus disappeared immediately after the minimum duration. Otherwise, the stimulus disappeared as soon as the subject gave the response or, in case no response was given, after the maximum duration. The next stimulus was presented after a blank screen lasting 500 ms. The resulting maximum block duration was 24 s. A variable additional period of visual fixation was added after the last stimulus of the block to compensate for responses shorter than 5500 ms and control the blocks onset time. A fixation cross lasting between 8 and 12 s was presented between blocks. At the beginning and at the end of the runs a fixation cross was presented for 17.6 s and 17 s respectively. The total duration of each run was 457.6 s.

Before starting the experiment subjects underwent a training session outside the scanner with 6 additional trials for each task in order to familiarize with the experiment.

Imaging data acquisition

Brain images were collected with a 4-Tesla Bruker MedSpec scanner (Bruker Inc., Ettlingen, Germany) using an 8-channel head coil. During the scanning sessions, the motor response was recollected using a fiber optic two button response pad (Cedrus, San Pedro, Ca, USA). The stimuli were back projected at the centre of the visual field

on an acrylic screen viewed by the subject through a mirror attached to the head coil using E-Prime software (Psychological Software Tools, Pittsburgh, PA, USA).

Functional images were acquired using a T2*-weighted gradient-echo echo-planar sequence (repetition time = 2200 ms, echo time = 33 ms, flip angle = 75°, acquisition matrix = 64 x 64, slice thickness = 3 mm, inter-slice gap = 0.45 mm, field of view = 192 x 192 mm, number of slices = 37). Each functional run had 208 brain volumes; at the beginning of each run five dummy scans were acquired.

For the subsequent superimposition of functional statistical parametric maps, a high-resolution structural 3D T1-weighted image was acquired (MPRAGE sequence, resolution 1x1x1 mm³, acquisition matrix 256 x 224; number of slices = 176; repetition time = 2700 ms, echo time = 4.18 ms, inversion time = 1020 ms).

Imaging data analysis

Preprocessing and data analysis were conducted using BrainVoyager QX 1.9 software package (Brain Innovation, Maastricht, The Netherlands).

Functional images from each subject were corrected for slice time acquisition with cubic spline interpolation. All volumes were realigned using a 3D rigid-body spatial transformation to the first volume of the first functional run. Temporal filtering included linear trend removal and a 0.028-Hz (5 cycles in time course) high pass filter to eliminate low frequency noise. The functional data were co-registered to structural images and they were spatially smoothed using a Gaussian kernel (full width at half maximum = 4 mm) and resampled to 2x2x2 mm voxels. The structural and co-

registered functional data were normalized into standard stereotaxic space (Lancaster et al., 2000).

Statistical analysis was performed using a multi-subject general linear model random effect analysis in BrainVoyager QX 1.9 software.

A regressor for each set of the four types of trials (W-AnR, P-AnR, W-Sem and P-Sem) was created for each functional run and convolved with a standard hemodynamic response function. Scans acquired during visual fixation were considered as baseline. The regressors of all subjects were used to implement a multi-subject GLM random effect analysis. Z-transformation was used for normalization of signal respect to the baseline. Six motion regressors (3 translation and 3 rotation parameters) on x, y, z axes were included in the analysis as covariates of no-interest. Also RT and semantic distance were added as covariates to remove BOLD signal variation correlated with the response time and/or the semantic distance among items.

The beta maps obtained from the GLM analysis were entered into a 2 x 2 ANOVA design: [Task (AnR; Sem) x Context (Word; Picture)]. The resulting statistical parametric maps were corrected for multiple comparisons using the false discovery rate (FDR) approach with $q < 0.005$ and excluding all clusters extending less than 0.2 cubic centimeters. The sets of clusters of voxels found to be significantly activated after this statistical correction were used to define regions of interest (ROI) on which to perform post-hoc t-tests.

The Talairach Client software (Lancaster, et al., 2000) was used to assign Talairach Atlas labels for a given x,y,z coordinate, represented by the center of gravity of each cluster of activation.

Results

Behavioural in-scanner results

Mean accuracy was 94% and 90% for the Sem and the AnR task respectively (Picture-AnR: mean 90%, sd 6%; Word-AnR: mean 89%, sd 7%; Picture-Sem: mean 93%, sd 6%; Word-Sem: mean 96%, sd 3%). The ANOVA for repeated measures revealed that accuracy was significantly higher in Sem task respect to AnR ($F[1,14]$ = 11,06; $p<0.004$). No effect for context was found ($F[1,14]$ = 0.7; $p=0.41$) and no interaction between task and context was present ($F[1,14]$ = 1.33; $p=0.27$).

The ANOVA for repeated measures revealed that the response time (RT) in Sem tasks was significantly faster than in AnR tasks ($F[1,14]$ = 268.26; $p<0.00001$). A significant effect of context was present with faster RTs for pictures ($F[1,14]$ = 9,7621; $p=0.007$). No interaction was found between task and context ($F[1,14]$ = 1.2062; $p=0.29$).

fMRI results

The fMRI results are summarized in Table 2.1 and 2.2 at the end of the section.

The context effect revealed that the pictures respect to the words were associated with greater activation in a bilateral set of posterior regions, including primary and associative visual areas, extending to parietal lobe and to paralimbic regions. Additional activations were found in the left superior parietal lobule and precuneus and in the right frontal lobe (inferior frontal and postcentral gyrus).

The words respect to the pictures were associated with greater activation bilaterally in the middle and superior temporal gyrus (but more extended on the left

side and in the left postcentral gyrus. Additional activations were found in the right

cerebellum and the right medial frontal gyrus (Figure 2.2 and Table 2.1).

Figure 2.2 Word *vs* Picture Context
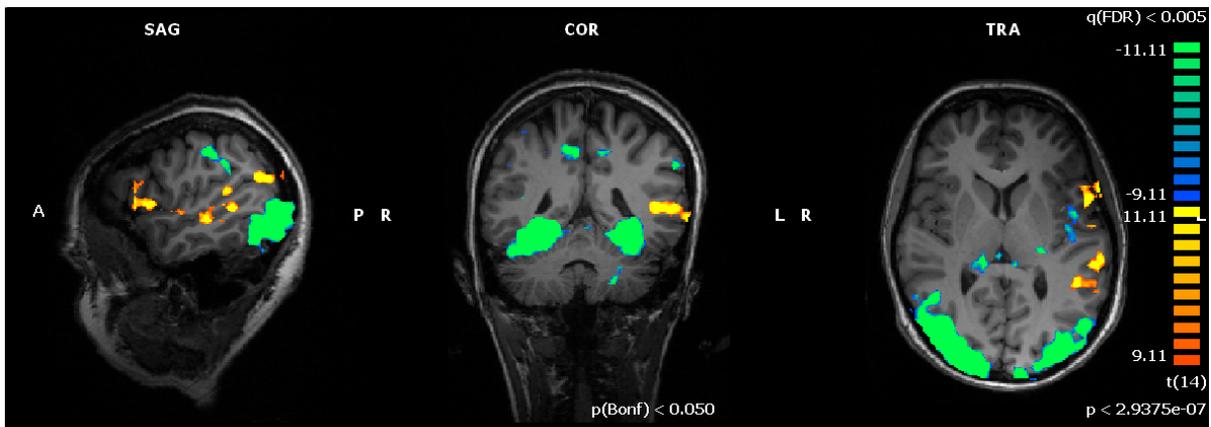
Statistical parametric map of the t-contrast between Word *vs* Picture context displaying areas responding to words (orange-yellow) and pictures (blue-green) context thresholded at q(FDR) <0.005.

Regions that showed increased activation during solution of analogical reasoning

task were found on parietal, temporal, frontal and paralimbic regions, with a clear

lateralization on the left hemisphere. In particular, analogical reasoning evoked greater

activations in the left fusiform gyrus (BA 37), left parahippocampal gyrus (BA 27), the

posterior part of left middle temporal gyrus (BA 22 and 39), the left middle frontal

gyrus (BA 9 and BA 46) and in the posterior portion of the left inferior frontal gyrus

(BA 45) (Figure 2.3 and Table 2.2).

Figure 2.3 Analogical Reasoning *vs* Semantic judgment
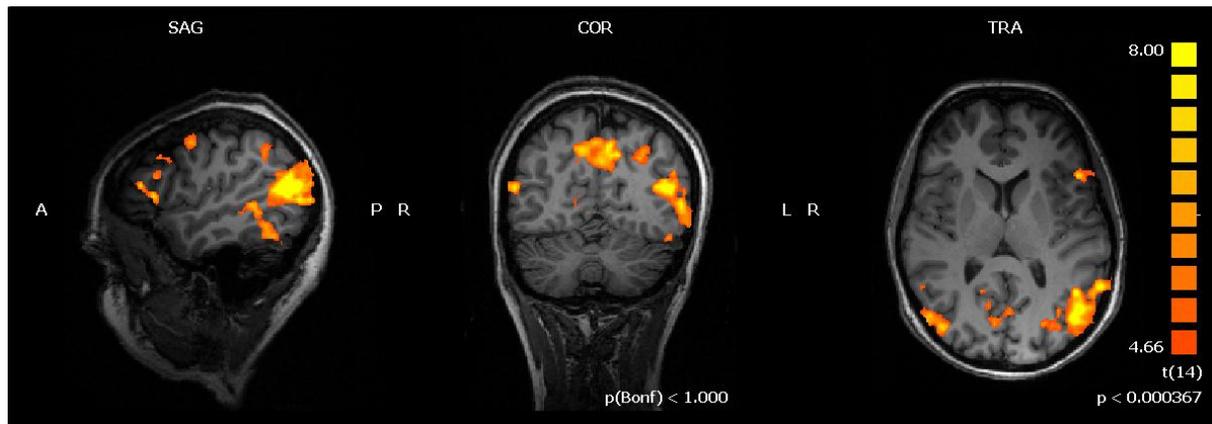
Statistical parametric map of the t-contrast between Analogical Reasoning *vs* Semantic judgment task showing areas responding to analogical reasoning thresholded at q(FDR) <0.005.

Notably, no areas displayed an interaction between task and context. Only raising the statistical threshold (FDR q=0.05) revealed an interaction between the two factors bilaterally in occipital lobe (Lingual gyrus) and in the parahippocampal gyri.

To asses the influence of context on analogical reasoning, we performed a separate ROI analysis. We focused the attention on three sets of regions that we found activated: prefrontal areas found more active in the AnR task, which the literature indicate as potential core areas for reasoning (BA9, BA46), verbal language areas (posterior part of IFG - BA 45, BA 44 and the posterior part of superior temporal gyrus – pSTG, BA22) and regions (left fusiform gyrus - BA37, posterior middle temporal gyrus –pMTG) that have been linked to conceptual-semantic competences (Bookheimer, 2002; Chao, Haxby, & Martin, 1999; Martin, 2007).

The specific ROI definition was based both on functional and anatomical criteria. The ROIs were selected within the voxels activated by analogical reasoning respect to

semantic judgment (NV-AnR + V-AnR *vs* NV-Sem + V-Sem). Only the BA44 was defined within voxels activated by words *vs* pictures contrast. The resulting regions of activity were then intersected with anatomical masks using the Talairach Client software (Lancaster, et al., 2000) in order to include in the analysis only the voxels belonging to the anatomical regions indicated by the centre of gravity of each cluster of activation, excluding voxels belonging to adjacent regions. The stereotaxic coordinates of pMTG were selected on the basis of previous research on picture and word processing (see Lin et.at. 2011 for a systematic review of functional neuroimaging studies).

The ROI analysis revealed distinct patterns of activity within these sets of regions (mean beta values and standard deviations are reported in the graphs of Figure 2.4).

The pre-frontal areas (BA9 and BA46) showed an involvement in both AnR and Sem task but with significant higher response during the former one (AnR *vs* Sem: BA9 p=0.02; BA46 p 0=0.0008). Notably, these areas were involved to a similar extent in word and picture contexts (Words *vs* Pictures: BA9 p=0.1; BA46 p=0.3). Despite the relative distribution of beta values within linguistic-semantic regions (left fusiform gyrus -BA37, and the pMTG) was different from that found in prefrontal areas, it revealed that also in these areas response was higher for analogical reasoning respect to semantic judgment (AnR *vs* Sem: BA37 p= 0.0002, pMTG p=0.002), without significative differences between words and pictures contexts (Words *vs* Pictures: BA37 p=0.25, pMTG p=0.69).

The posterior IFG (BA44) and pSTG (BA22) were influenced by stimulus properties (context dependent response), being active almost exclusively in the word

context (Words *vs* Pictures: BA44 p=0.01, pSTG p=0.69). While BA44 did not show differential activation between tasks, BA22 showed a significant higher response in analogical reasoning (Wors-AnR *vs* Word-Sem: p= 0.0001).

The only region that showed a selective increased activity for analogical reasoning not significantly dependent from the context was the anterior part of inferior frontal gyrus (BA 45)(Words *vs* Pictures p=0.32; AnR *vs* Sem p=0.0001) .

Figure 2.4 shows plots of mean normalized beta values for the four types of regressors in each ROI selected.

Figure 2.4 ROI Analysis
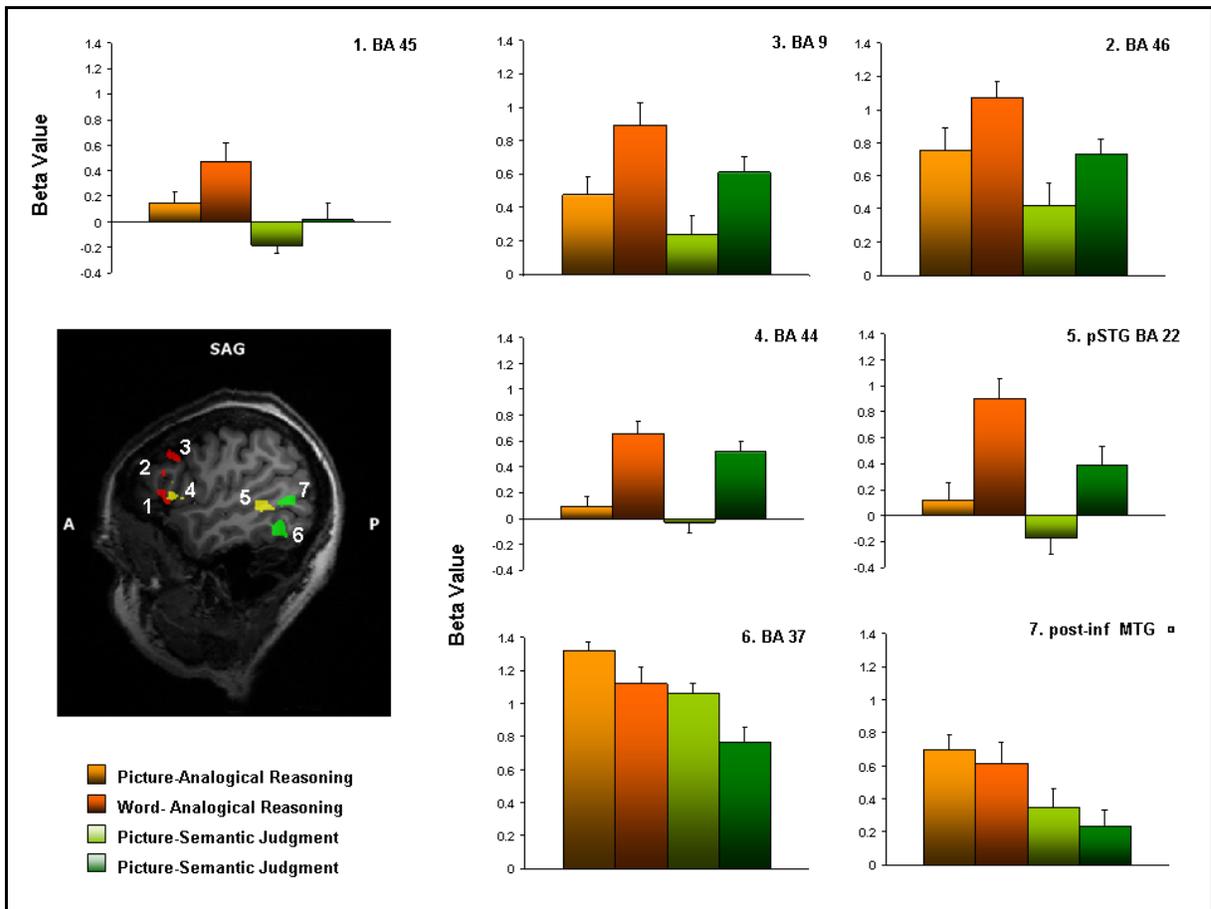
ROI analysis of the left areas found activated during Analogical Reasoning tasks described in the results section. The plots depict the mean normalized beta values for the four conditions. Abbreviations: BA = Brodmann Area.

Table 2.1 Context Effect

Area	Talairach Coordinates			Nr of Voxels	BA
	x	**y**	**z**		
Picture *vs* Word Context					
Bil. Occipital & Post. Inf.Temporal Lobe	6	-62	-0.6	111718	18/19/37
L Ant Cingulate Gyrus	0.27	-1.8	37	1200	24
L Precuneus	-20	-68	45	1593	7
L Middle Frontal Gyrus	-27	22	49	812	8
L Insula	-39	-12	4.2	410	13
L Inferior Parietal Lobule	-53	-31	35	3713	40
R Inferior Frontal Gyrus	48	-0.79	22	737	9
R Postcentral Gyrus	46	-25	40	2758	2
R Putamen	31	-6	-2.6	830	
Word *vs* Picture Context					
L Superior Temporal Gyrus	-48	-61	21	1537	39
L Precentral / Inf. Frontal Gyri	-51	13	9.3	714	44
L Middle Temporal Gyrus	-53	-31	2.1	4147	22
R Superior Temporal Gyrus	49	-33	0.073	1259	22
R Superior Temporal Gyrus	40	-54	29	663	39
R Medial Frontal Gyrus	7.2	36	38	462	8
R Cerebellum	20	-73	-36	3665	

Table 2.2 Task Effect

Area	Talairach Coordinates			Nr of Voxels	BA
	x	**y**	**z**		
AnR *vs* Sem					
L Precuneus-Sup Parietal Lobule	-26	-65	27	39918	7/19/30
L Posterior Cingulate	-1	-58	27	697	31
L Parahippocampal Gyrus	-22	-33	-8	364	27
L Fusiform Gyrus	-45	-50	-14	664	37
L post Middle Temporal Gyrus - Angular Gyrus	-42	-65	20	7332	21/37/39
L Middle Temporal Gyrus	-54	-44	2.4	1090	22
L Precentral Gyrus	-33	-6.5	51	3871	6
L Inferior Frontal Gyrus	-49	23	9.7	545	45
L Middle Frontal Gyrus	-43	19	20	321	46
L Middle Frontal Gyrus	-49	15	33	224	9
R Lingual Gyrus	13	-85	4.2	502	17
R Superior Occipital Gyrus	36	-71	22	519	19
R Middle Temporal Gyrus	35	-67	22	3144	39
R Middle Temporal Gyrus	51	-41	-2.2	298	22
R Superior Temporal Gyrus	49	-8.6	-8.7	247	22
Bilateral Lingual Gyrus	-7	-77	-3	3893	18

Discussion

In the neuroscience field, converging experimental evidences indicate that a network of areas within the left hemisphere is critically involved in analogical reasoning, indicating the prefrontal cortex as the core region. The left hemisphere is dominant for language in 95% of the normal adult population. Despite there is a general agreement on the strong relationship between language and reasoning (Baldo, et al., 2010; Gentner, 2003; Gentner & Christie, 2010), it is not clear how much the verbal degree of the context influences the activity of this network. In this experiment we assumed that when reasoning is performed on words the phonological-lexical system is mandatory to access the meaning, while when reasoning is performed on meaningful pictures lexical/phonological processing may be triggered, but it may be not mandatory to the reasoning itself.

In the present investigation, we presented the arguments for analogical reasoning within either a word or a picture context: our 2x2 design allowed us to verify the different contribution of the language system to reasoning as a function of the context.

Our results confirmed that the left hemisphere plays a central role in relational reasoning. In fact, analogical reasoning evoked activity in a clearly left lateralized circuit including the fusiform gyrus, the parahippocampal region, the posterior part of the superior temporal gyrus, the middle and inferior frontal gyri. These activations are consistent with previous neuroimaging studies indicating that analogical reasoning engages a neural network comprising both anterior and posterior regions in the left hemisphere (Bunge, et al., 2005; Geake & Hansen, 2005; Goel & Dolan, 2004; Kroger, et

al., 2002; Luo, et al., 2003; Wendelken, Nakhabenko, Donohue, Carter, & Bunge, 2008; Wharton, et al., 2000).

Interestingly, most of the areas we found more active during analogical reasoning compared to semantic judgment did not show any context effect. The strong activations found in the left dorsolateral prefrontal cortex - DLPFC (BA 9 and 46) confirmed lesion and neuroimaging studies indicating a critical role of these areas for reasoning (Bunge, et al., 2005; Goel & Dolan, 2001, 2003, 2004; Green, et al., 2010; Hampshire, et al., 2011; Krawczyk, et al., 2011; Monti, et al., 2009) in particular when it requires active manipulation and monitoring of information within working memory (Petrides, 2000; Ramnani & Owen, 2004). Previous studies suggested that, during analogical reasoning, activity of DLPFC is independent from intra-task features such as associative strength or number of relations to be considered (Bunge, et al., 2005; Christoff, et al., 2001; Kroger, et al., 2002; Wharton, et al., 2000). In addition, the results suggested that the complex processing performed by this region is also independent from the context, since BA9 and BA46 appeared equally activated in both analogy tasks. This is in keeping with the idea that frontal cortex is organized according to the nature of processing required rather than to the modality of the information to be processed (Owen, 1997; Petrides, 1994; Petrides, Alivisatos, & Evans, 1995).

Also areas traditionally linked to semantic system (Bright, Moss, & Tyler, 2004; Chao, et al., 1999; Martin, 2007) showed a higher response during analogical reasoning, independently from the context. The context-independent response of pMTG and fusiform gyrus confirmed previous neuroimaging data which indicate that these regions respond both to picture and to written words and their activity is modulated

mainly by the semantic category of the items (Chao, Weisberg, & Martin, 2002; Lin, et al., 2011; Mahon et al., 2007; Martin, 2007). This observation has been used to support the idea that the semantic system is organized in the brain in a unitary fashion and can be accessed independently from the stimulus properties (Bright, et al., 2004; Caramazza, et al., 1990) and our results are in agreement with this idea.

The pattern of activity of the anterior part of the inferior frontal gyrus (BA 45) not only did not display any context effect but appeared also to be specific for analogical reasoning remaining almost silent during the semantic task within both contexts. This result do not agree with the idea of BA45 being involved in the semantic retrieval per se (Bookheimer, 2002) while it supports the hypothesis that the anterior IFG specifically subserves the selection of task-relevant knowledge amidst competing irrelevant knowledge (Kimberg & Farah, 1993; Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001). In fact, if BA45 mediates only the semantic retrieval, it might be expected its involvement also during the semantic judgment condition. The selective activation found during analogy suggests that it is engaged when it is necessary to control the search/selection/recovery of semantic properties (Whitney, et al., 2009) relevant for the reasoning to be performed. On the other hand, it must be taken into consideration that BA45 is modulated by the semantic distance among items (Bunge, et al., 2005; Hampshire, et al., 2011). In our analysis we factor out this element introducing the semantic distance as a confound covariate. Thus, it is possible that part of the activity within BA45 related to the semantic judgment has been "canceled". Even if this would be the case, so that an involvement of BA45 for the semantic judgment per se cannot be

fully excluded, still our data suggest that the activity during analogical reasoning is not explained by a simple semantic retrieval. Instead, we suggest that its activity must be related to some additional operation to be performed when semantic knowledge has to be manipulated to perform relational reasoning, for example selecting the stimuli-related knowledge relevant in order to find the only one which allows solving the analogy.

The only strong context effect was evident in the pSTG and IFG (BA 22 and BA 44), brain areas considered critical for lexical and phonological processing (Graves, Grabowski, Mehta, & Gupta, 2008; Heim, Eickhoff, & Amunts, 2008): strong activation of these areas was evident whenever the task was performed with words and, notably, their activity was linked almost only to the word context. Thus, it may be assumed that the activity in these areas was just due to inner verbalization/speech strongly triggered by words and not needed when analogical and semantic reasoning was performed on pictures. Nevertheless, the pSTG displayed an additional modulation being significantly more active during analogical reasoning. Based on this observation, we cannot rule out that, when the activation was triggered by words, the processing performed by this area may have specifically contributed to reasoning. Although part of the pSTG response has been linked to the phonological access (Graves, et al., 2008), the exact functional organization of this region and of the adjacent areas of superior temporal sulcus is not fully understood. It has been suggested that they subserve also the process of cross-modal binding (Beauchamp & Martin, 2007; Hocking & Price, 2008) and the integration of lexical-semantic information (Friederici, Makuuchi, &

Bahlmann, 2009). It is reasonable to hypothesize that this last function may help the process of analogical reasoning especially when it is performed within a word context.

Overall, these data are consistent with the idea of a sovra-modal system subserving reasoning. When the system has to work on words, this triggers the engagement of language structure as an additional step (e.g. lexical-phonological system). However, it is possible that the triggering of the lexical-phonological system may influence the performing of the reasoning itself, as demonstrated by the significantly increased activity in the pSTG during analogical reasoning. In order to better understand how these areas are coordinated further investigations should be carried out with electrophysiological technique, such as Transcranical Magnetic Stimulation (TMS) or Magneto-electroencephalography (MEG). This would allow to estimate the effect of inhibition and/or facilitation among them and the timing of activation: if the pSTG plays a specific role in reasoning it could be expected that it will be active not only in the early phase in relation with phonological access required by reading but also at a later stage as for BA45. On the other hand, our data suggest also that analogical reasoning may be performed without the involvement of lexical-phonological components. When analogical reasoning was performed on pictures, in fact, we did not observe any clear involvement of BA44 and/or BA22 (pSTG). Interestingly, we did not use any picture (or word) referring to abstract concepts. It is possible to argue that visual information conveyed by a picture of a concrete item is sufficient to perform an analogy among items without passing through any verbal label. This hypothesis is compatible with the experimental data available in the

literature (Bright, et al., 2004; Caramazza, et al., 1990; Saffran, et al., 2003). We suggest that visually presented object directly access the semantic knowledge under the top-control of prefrontal regions, while words require also a phonological and lexical analysis and integration, as documented by the selective activation of BA44 and BA22. In this respect, the picture of a concrete item may directly activate the semantic system from which information may flow directly to the working memory and analogical reasoning apparatus, without requiring a covert verbalization strategy especially if a limited time is available for the response. The faster RTs in picture context also support this hypothesis of a more direct elaboration of meaningful pictures.

Results from this study do not allow a final response to the possible role of verbal strategies, in particular covert verbalization, in analogical reasoning: it is possible that, provided with more time for the response, the healthy adults may rely also on a different strategy to ensure the correct solution of analogy, passing through a covert verbalization of pictures and/or relational terms. In addition, the analogy problems used in the present experiment were easy and related to concrete objects and relationships: it could be supposed that increasing the difficulty of the task, for example introducing abstract meaningless figure or/and multiple simultaneous relations between stimuli, may prevent the solution of the task based only a direct access to semantic information.

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Brain activity during analogical reasoning in language impaired subjects: the case of developmental dyslexia

Developmental dyslexia is a persistent problem that involves a serious difficulty in identifying written words. This problem affects people of otherwise normal intellectual capacity and it is characterized by difficulties with accurate and/or fluent word recognition and by poor spelling and decoding abilities. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, 2000) this learning disorder involves substantially lower reading performance than expected according to the child's chronological age, intelligence, and school grade.

Despite there is a general consensus on considering developmental dyslexia a disorder with a neurobiological origin (Ramus, 2004), in the last years various theories of dyslexia have been proposed in order to understand and better define this learning disability which, in addition to the reading impairment, seems to be associated with problems in phonology, sensory difficulties in visual, auditory and tactile domains (see Ramus , 2003 for a review).

The majority of evidences coming from different lines of investigations indicate that developmental dyslexia represents a disorder within the language system, and in

particular in the phonological processing. The phonological theory (Snowling, 2000) postulates that the developmental dyslexia is linked to an impairment in language domain characterized by deficit in the representation and processing of speech sounds which causes difficulty in learning and handling the grapheme–phoneme correspondence.

Both anatomical and functional studies support the idea that developmental dyslexia is linked to an impairment of language systems. Postmortem, brain morphometry and diffusion tensor imaging (DTI) studies have documented many structural differences between dyslexic and control brains within the language network both in gray and white matter organization (Eckert, 2004). Geschwind and Galaburda indicated that dyslexics' brain showed a peculiar hemispheric asymmetry due to a smaller left hemisphere associated with a larger right one (Geschwind, 1987). In addition, Galaburda et al. (1985) observed anomalies of cell migration, such as small foci of ectopia and microgyria, located in the left perisylvian cortex, associated with an asymmetry of planum temporale. Recently, areas of decreased fractional anisotropy have been reported in relation to the perisylvian language network in dyslexic children (Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010; Steinbrink et al., 2008).

Functional neuroimaging studies suggest a different brain organization not only at a structural level, but also at a functional one. In particular, dyslexics showed less activation in the left hemisphere within inferior frontal gyrus, superior temporal gyrus, occipito-temporal areas, with the additional recruitment in dyslexics of right frontal regions across reading and phonological tasks (S. E. Shaywitz & Shaywitz, 2005; Temple et al., 2000).

Independently from the approaches to dyslexia and the cognitive domains explored, the majority of the literature focused the attention on the search and explanation of the nature of the deficit associated to developmental dyslexia, but evidences also suggest that developmental dyslexia is a more complex picture. In fact, despite the deficit in various domains, evidences support the idea that the dyslexia could be linked to a talent in the non-verbal domain that may partly compensate the language difficulties (Bacon & Handley, 2010; Miles, 1993). Davis (1997) has proposed that individuals with dyslexia engage in internal monologue using the semantics (or image of meaning) of words. Since the earliest description of dyslexia at the beginning of 19th century, it has been suggested that it could be associated with spared or enhanced visuo-spatial abilities. Orton (1925) suggested that dyslexia may sometimes be accompanied by spatial talents. Similarly, Geschwind and Galaburda (1987) noted a high incidence of individuals with dyslexia in professions requiring spatial abilities, such as art, engineering, or architecture. And there is a growing popular view that dyslexia is associated with compensatory talents in the visual-spatial arena that allow individuals with dyslexia to excel in professions that capitalize on such strengths (e.g., computer graphics) (West, 1997; Winner et al., 2001).

However, data reported in the literature are not consistent. Winner et al. (2001) documented that in a wide range of visuo-spatial tasks, dyslexics performed just as well as or even poorer respect to normal readers; Morris et al. (1998) documented a relative weakness in a subgroup of dyslexics in non-verbal domains. Conversely, other evidences support the hypothesis of a non-verbal talent in developmental dyslexia. Dyslexics were shown to be superior at rapidly discriminating between drawings of

impossible versus possible figures (von Karolyi, 2001). Recently, it has been documented that dyslexia is associated with enhanced abilities in visuo-spatial processing (von Karolyi, Winner, Gray, & Sherman, 2003) and in the implicit learning processing in spatial context (Howard, Howard, Japikse, & Eden, 2006). Trauzelttel-Klosinki et al. (2006) underline that children with developmental dyslexia are faster and more accurate respect to controls in naming meaningful pictures suggesting a direct access to the semantic system mediated by pictures. Looking at higher cognitive functions, the literature offers few and discordant data about the executive functions in developmental dyslexia. Nevertheless, there are evidences which suggest that in dyslexics planning and problem solving abilities may be better respect to the normal readers (Brunswick, Martin, & Marzano, 2010; Reiter, Tucha, & Lange, 2005). It has been documented that, in visual reasoning, dyslexic participants are more accurate and adopt different modalities to solve inference problems: dyslexics adopt strategies involving visuo-spatial representations, while non-dyslexics tend to use abstract verbal strategies (Bacon & Handley, 2010; Bacon, Handley, & McDonald, 2007).

Altogether the literature data suggest that dyslexics 1) have a cognitive talent for non-verbal domains; 2) rely on different reasoning strategies and 3) have a different neural brain organization both at structural and functional level respect to normal readers.

In this work we try to understand if there is a relationship between these three evidences through a neuropsychological assessment and a functional MRI investigation.

The neuropsychological investigation allows to explore if the non-verbal domain, and in particular problem solving and reasoning, may be considered a talent of dyslexics respect to unimpaired readers. It is also possible that dyslexics show only a relative sparing of these competences respect to their verbal and reading skills, but not a real superiority respect to normal readers.

In the functional MRI study, we expected that if the non-verbal domain is a real (or even relative) talent of dyslexics, they may have performed reasoning (specifically an analogical reasoning task) using different strategies, more related to visual modalities, which should find their counterpart at a functional level with a different involvement of brain areas related to reasoning itself.

In the previous study on adult normal readers, we documented that analogical reasoning is a left hemisphere phenomenon, where the load of language related areas is modulated by the context within which reasoning is performed. In particular, only reasoning on word context evoked a greater activity in core areas known to be involved in lexical-phonological processing, i.e. BA 44 and BA 22 (Graves, et al., 2008; Heim, et al., 2008).

It could be hypothesized that dyslexics may show brain reorganization secondary to the reading disability. In the case of deep reorganization, analogical reasoning may evoke a completely different pattern of activity. For example a possible involvement of the right hemisphere may be expected since it mediates non-verbal abilities and it has been proposed to be a possible compensatory system (S. E. Shaywitz & Shaywitz, 2005). A second possibility is that dyslexics may differ from normal readers only when analogical reasoning is performed on pictures displaying a brain activity pattern less

lateralized, typical of early and middle infancy (Moses et al., 2002) when verbal strategies are much less used by the child.

The third possibility that we have taken into account is that reading disability induces a more subtle reorganization where the context within which reasoning is performed modulates the activity of the areas involved in reasoning. In this case, it may be supposed that the major differences will be found in language areas within the word context. On the basis of the results of the previous study, we expected that those areas which were not modulated by the context, i.e. anterior part of inferior frontal gyrus (BA45), fusiform gyrus, prefrontal cortex, during the reasoning task would display a similar pattern of activity in dyslexics as in normal readers.

In the first study it has been argued that pictures of concrete items may directly access to semantic knowledge and to reasoning-dedicated areas, without requiring the load of verbal areas. If this is the case, we supposed that this phenomenon may be particularly accentuated in dyslexics configuring a possible cognitive advantage.

Material and Methods

Subjects

The young subjects recruitment was performed following the procedure approved by the Ethics Committee of the University of Trento. Only children and adolescents older than 12 years were admitted to the study: in fact there is a general consent, supported by the physiological development of cognitive functions, that 12 year old children (or older) have the possibility to give their consent to the participation understanding the responsibility of this choice (Gill, 2004).

After the preliminary contact with the participants, the investigator had to inform the family doctors about the possible participation in the experiment and organized a preliminary visit to the Functional Neuroimaging Lab in order to allow young participants and their family to understated the aim of the study, ask any additional information, familiarize with the experimental setting and procedure. In this occasion the investigator had to ensure that the child was not forced to participate in the experiment by parents and explained to potential participants that no clinical diagnostic advantage could be derived by the participation in the research. After this phase, both parents signed an informed consent form and the subsequent steps (i.e. neuropsychological evaluation and fMRI experiment) of the study could be programmed. Participants were allowed to give the consent for only one of the two phases of the study.

Overall, 25 subjects have been recruited for this study: 14 children with a diagnosis of developmental dyslexia and 11 normal readers without history of neurological or developmental disorders. All participants were Italian native speakers.

Developmental Dyslexia (DD) Group: 14 young potential participants were recruited (12 males and 2 females; mean aged 15 years old, range 13-19). One potential participant was excluded from the study because of comorbidity with a relational disorder. Two of them participated only in the neuropsychological evaluation because MRI incompatible and absence of parent's consent for fMRI procedure. One child was excluded from fMRI data analysis because of head and legs movement artifacts. Thus, the final sample for the fMRI experiment was composed by 10 subjects (9 males and 1 females; mean age: 15 years, range: 13-19), while 13 subjects participated in the neuropsychological evaluation.

Normal Readers (NR) Group: 11 young participants were recruited for the study. After the preliminary visit to the neuroimaging lab, two children were excluded because of MRI incompatibility or absence of one parent's consent for the procedure. One subject participated only in the neuropsychological evaluation because of MRI incompatibility.

Overall, 8 young participants (2 male and 6 females; mean aged: 15 years, range 13-19) participated in the MRI experiment. Five of them refused to participate in the full neuropsychological assessment and were tested only to assess their reading skills. Overall, only three subjects participated both in the fMRI experiment and in all

neuropsychological evaluation. In order to have numerosity homogeneity between groups, during the analysis the data of two young adults (less than 22 years old) were added to the NR group. Thus, the NR sample for the fMRI experiment was composed by 10 subjects (4 male and 6 females; mean aged 16 years, range 14-21).

Neuropsychological assessment

The neuropsychological evaluation focused on non-verbal abilities and higher executive functions (planning, problem solving). The entire protocol was made of well-known, standardized tests for the study of intelligence, memory, visual-spatial skills, reasoning and problem solving.

All the children were administered the Wechsler Intelligence Scales -WISC-III (Wechsler, 1991) to assess the cognitive abilities.

The reading skills were assessed using the standardized Italian reading tasks for evaluation of reading abilities (Cornoldi & Colpo, 1995; Sartori, 2007). In particular we considered the following parameters: reading comprehension, reading speed and accuracy of words, pseudowords and text.

The planning and problem solving were evaluated with the Raven's Progressive Matrices - RPM (Raven, 1962), the Wisconsin Card Sorting Test -WCST (Stuss et al., 2000) and Maze and Block Design subtests of WISC-III which are considered, within the scale, tasks sensible to planning and problem-solving.

Memory was assessed using the Test of Memory and Learning -TOMAL (Reynolds, 1994) which is a comprehensive battery of 14 memory and learning sub-tests, divided into the content domains of verbal and non-verbal (visual) memory,

which can be combined to obtain a verbal memory index (VMI) and a non-verbal memory index (NVMI).

Visuo-spatial abilities and visuo-motor integration were evaluated with the Beery's Visuo-Motor integration test (Beery, 1967), which requires copying of geometrical figures with increasing difficulties, and with the Rey-Osterrieth Complex Figure test (Osterrieth, 1944) which required the subject to reproduce a complex line drawing.

Verbal working memory was assessed using the digit span backward and forward subtests of TOMAL which evaluated the short-term auditory memory. The visuo-spatial non-verbal working memory was assessed with two subtests of TOMAL (Memory for Location; Visual Sequencing Memory) and the Coding subtest of WISC scale which required also the automatization process of the procedure.

fMRI experiment

The fMRI assessment (stimuli, tasks, fMRI design and procedure, data acquisition) was the same as for the first study previously described (see Chapter II).

Imaging data analysis

Preprocessing and data analysis were conducted using BrainVoyager QX 1.9 software package (Brain Innovation, Maastricht, The Netherlands).

Functional images from each subject were corrected for slice time acquisition with cubic spline interpolation. All volumes were realigned using a 3D rigid-body spatial transformation to the first volume of the first functional run. Temporal filtering

included linear trend removal and a 0.028-Hz (5 cycles in time course) high pass filter to eliminate low frequency noise. The functional data were co-registered to structural images and they were spatially smoothed using a Gaussian kernel (full width at half maximum = 4 mm) and resampled to 2x2x2-mm^3 cubic voxels. The structural and co-registered functional data were normalized into standard stereotaxic space (Talairach & Tournoux, 1988).

Statistical analysis was performed using a multi-subject general linear model random effect analysis in BrainVoyager QX 1.9 software. A regressor for each set of the four types of trials (Picture-AnR, Word-AnR, Picture-Sem and Word-Sem) was created for each functional run and convolved with a standard hemodynamic response function. Scans acquired during visual fixation were considered as baseline. The regressors of all subjects were used to implement a multi-subject GLM random effect analysis. Z-transformation was used for normalization of signal respect to the baseline. Six motion regressors (3 translation and 3 rotation parameters) on x, y, z axes were included in the analysis as covariates of no-interest.

Beta maps were generated for each subject for each of the following contrast: Word *vs* Picture; AnR *vs* Sem; Word-AnR *vs* Picture-AnR. The beta maps of each subject for each contrast of interest obtained from the GLM analysis were entered into the ANOVA design to explore the influence of task and context within and between groups.

The resulting statistical parametric maps were corrected for multiple comparisons using the false discovery rate (FDR) approach with q < 0.05 and excluding all clusters extending less than 0.2 cubic centimeters.

The Talairach Client software (Lancaster, et al., 2000) was used to assign Talairach Atlas labels for a given x,y,z coordinate, represented by the center of gravity of each cluster of activation.

Results

Neuropsychological evaluation

Only the data of DD group are presented because the NR group in this phase of study did not reach a significant numerosity (4 subjects).

The scores obtained from the different tests were converted in z-scores (standard score WISC-III, RPM, TOMAL, WCST, VMI Mean = 100; StandardDev = 15; standard score for subtests Mean = 10; StandardDev = 2). Table 3.2 and figure 3.1 reports the performances on the different test used grouped by the cognitive domain examined. Performances lower than 2 sd below the average were considered impaired; performances ranging from -1 sd to -2 sd were considered borderline; performances ranging from -1 to +1 sd were considered in the average; performances ranging from +1 to +2 sd were considered in the higher average.

As expected, considering the diagnostic criteria for developmental dyslexia, all children had general Intelligent Quotient (IQ) within the normal range associated with a reading impairment in at least two of the tests considered (reading words, pseudo words, text). The text comprehension was spared: only two dyslexic participants performed below the normal range. In the normal readers the performance in all tests

assessing the reading abilities was within the normal range. The results are reported in the Table 3.1

Table 3.1 Reading skills

|	NR		DD	
	mean	**sd**	**mean**	**sd**
Word				
Speed	0.42	0.51	-2.64	1.71
Accuracy	0.33	0.58	-1.78	0.78
Pseudo-Words				
Speed	0.50	0.58	-2.88	0.67
Accuracy	0.37	0.32	-1.94	0.58
Text				
Speed	0.25	0.56	-1.41	0.32
Accuracy	0.33	0.58	-0.75	1.30
Comprehension	0.67	0.53	-0.23	1.36

Concerning the verbal and the non-verbal abilities, all dyslexics showed a performance within the normal range in both domains, but with significant higher scores in the non-verbal one (WISC-III: Mean Verbal-IQ = 102, sd=9; Mean Performance-IQ = 111.5 sd= 10.6, with p =0.01; TOMAL; Mean Verbal Memory Index =99.8 sd=9.5; Mean Non-Verbal Memory Index =110.5 sd=9.5 with p=0.001): 7 out of 10 children showed a significant (p<0.01) difference between Verbal-IQ and Performance-IQ on WISC-III and between Verbal and Non-Verbal memory index of TOMAL. The visuo-spatial skills, evaluated with VMI and Rey's Figure, were in the normal range. Overall, the problem solving abilities scores were within the highest range of normal

values, with the only exception of Raven's Progressive Matrices whose score remained just within the normal limit. Borderline or low performances respect to the normal range were documented in tasks which implied verbal working memory load and in the Coding subtest of WISC-III.

The NR group, respect to dyslexics, showed higher performances in verbal domains and in tasks requiring an automatic processing (Coding) and working memory.

Notably, in the majority of the reasoning tasks it was possible to observe a trend: overall DD performed better than the controls.

Figure 3.1 Neuropsychological profiles of dyslexics and normal readers.
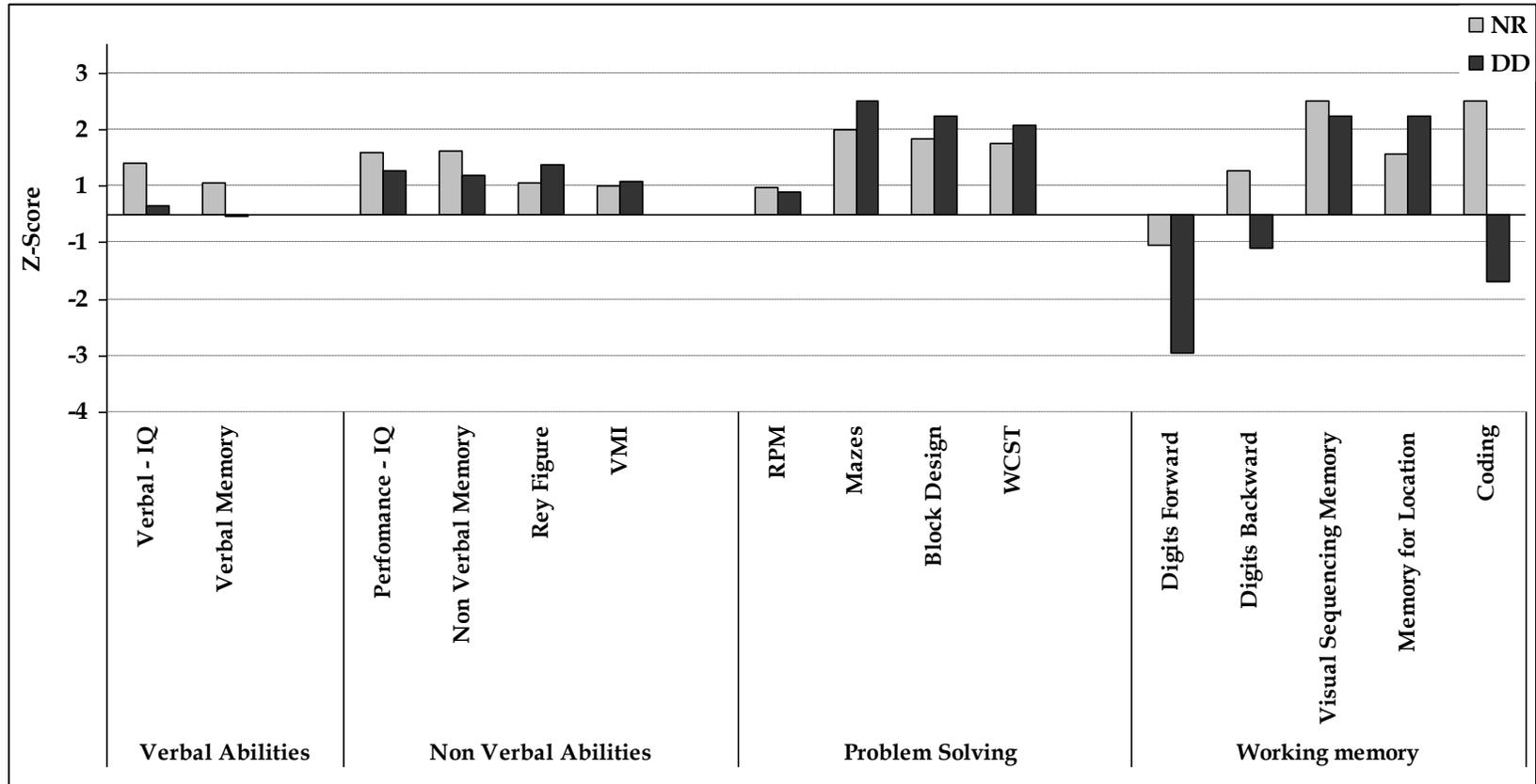
Abbreviations: IQ= Intelligence Quotient; VMI= Visuo-Motor Integration Test; RPM = Raven's Progressive Matrices; WCST = Wisconsin Card Sorting Test.

Table 3.2 Summary of neuropsychological results of dyslexics

	mean	sd	Qualitative Level
Verbal Abilities			
Verbal IQ - WISC-III	102.46	9.15	average
Informations	10.33	2.5	average
Similarities	10.67	2.55	average
Vocabulary	12.44	3.36	average
Comprehension	11.56	2.46	average
Arithmetic	10.89	1.96	average
Digit Span	8.25	2.66	borderline
Verbal Memory Index-TOMAL	99.85	9.57	average
Memory for Stories	11.18	2.32	average
Word Selective Reminding	11.23	3.35	average
Object Recall	11.69	2.18	average
Digits Forward	6.31	1.6	low average
Paired Recall	9.62	2.99	average
Digits Backward	9.08	2.02	average
Non-Verbal Abilities			
Performance IQ - WISC-III	111.46	10.62	average
Picture Completion	12.56	3.09	high average
Picture Arrangement	13.44	3	high average
Block Design	13.5	2.37	high average
Object Assembly	11.88	1.64	average
Maze	14	1.93	high average
Coding	8.22	3.03	borderline
Non-Verbal Memory Index - TOMAL	110.54	11.39	average
Facial Memory	11.54	2.79	average
Abstract Visual Memory	10.85	1.57	average
Visual Sequencing Memory	12.62	2.47	high average
Memory for Location	12.62	2.22	high average
Manual Imitation	10.5	2.2	average
Rey's Figure	113.27	5.61	average
VMI	108.69	10.87	average

(Follows)

Table 3.2 Summary of neuropsychological results of dyslexics

	mean	sd	Qualitative Level
Problem Solving/planning			
WCST- Total Error	123.62	13.02	high average
Perseverative Response	130.46	12.19	high average
Perseverative Errors	128	11.62	high average
No-Perseverative Errors	118.77	17.67	average
RPM	106.08	5.79	average
Block Design	13.5	2.37	high average
Maze	14	1.93	high average
Working memory			
Digit span	8.25	2.66	borderline
Digits Forward	6.31	1.6	low average
Digits Backward	9.08	2.02	average
Coding	8.22	3.03	borderline
Visual Sequencing Memory	12.62	2.47	high average
Memory for Location	12.62	2.22	high average

Behavioural in-scanner results

The mean response time (RT) was globally slower in DD respect to NR (DD. mean= 2621 msec, sd = 720 msec; NR: mean= 2194 msec, sd = 509 msec). The ANOVA for repeated measures revealed that the response time (RT) was faster in NR respect to DD ($F[1,18] = 7.28$; p=0.01). A significant effect of context was present with faster RTs in picture respect to word context ($F[1,18] = 59.00$; p<0.0001) with an interaction between context and group ($F[1,18] = 59.00$; p=0.001): DD group was significantly slower in word context respect to NR. No differences in RTs between groups were found in picture context (p=0.4). Also a significant effect of task was found with faster RTs in semantic judgment respect to analogical reasoning ($F[1,18] = 237.79$; p<0.0001) with an interaction with group ($F[1,18] = 7.04$; p=0.01). No interaction was found between task and context ($F[1,18] = 0.83$; p=0.37) .

Respect to the accuracy, ANOVA for repeated measures revealed that NR were more accurate respect to DD ($F[1,18] = 10.64$; p=0.004). A significant effect of context was present with a global better performance in picture context ($F[1,18] = 5.57$; p=0.02) with a significant context X group interaction ($F[1,18] = 7.22$; p=0.01): DD group was less accurate in word context. No differences in accuracy between groups were found in picture context (p=0.3). Also, a significant effect of task was found with higher accuracy in semantic judgment ($F[1,18] = 16.73$; p=0.0006). No interactions were found between task and group ($F[1,18] = 2.03$; p=0.1) and between task and context ($F[1,18] = 0.67$; p=0.42) .

fMRI results

The fMRI results are summarized in tables at the end of the results section.

Respect to picture context, the word in the NR was associated with a greater activation in left superior/middle temporal gyrus (BA22) and inferior frontal gyrus (BA45) (Fig.3.2.a and Table 3.3). Respect to the previous study on adults, the activations were more localized in the left hemisphere. In DD group, word context evoked activations involving medial structures, left precentral gyrus, the left inferior frontal gyrus and the left middle temporal gyrus (Fig.3.2.b and Table 3.4). In word context, NR respect to DD were associated with significant activation in the left inferior and middle frontal gyri; conversely, DD respect to NR engaged bilaterally the insula and the structures of the cingulate (Fig.3.3 and Table 3.5).

The picture context in both groups was associated with greater activation in a bilateral set of posterior regions, including primary and associative visual areas, extending to the parietal lobe and to paralimbic regions.

**Figure 3.2.a Word *vs* Picture Context in young normal readers**
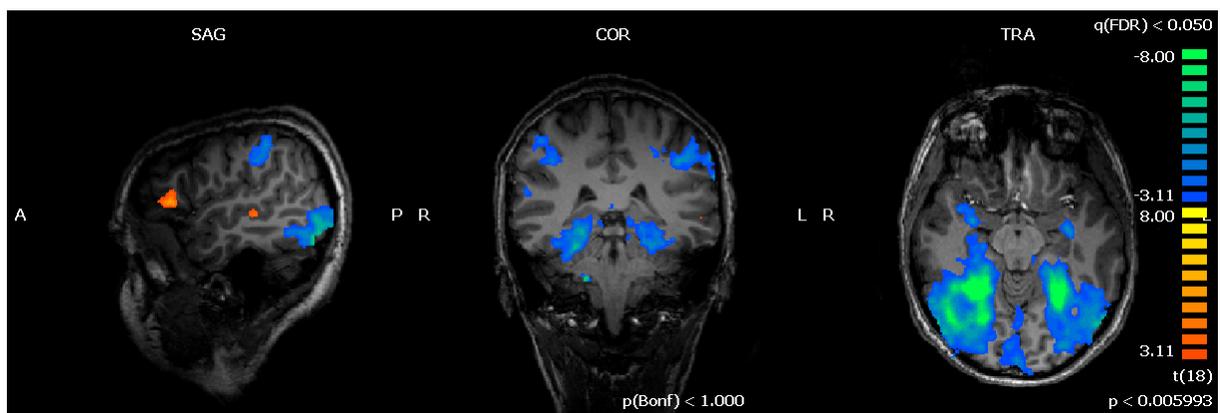
Statistical parametric maps of the t-contrast between Word vs Picture context thresholded at q(FDR) <0.05. Orange-yellow: areas responding to word context; blue-green: areas responding to picture context.

Figure 3.2.b Word *vs* Picture Context in young dyslexics
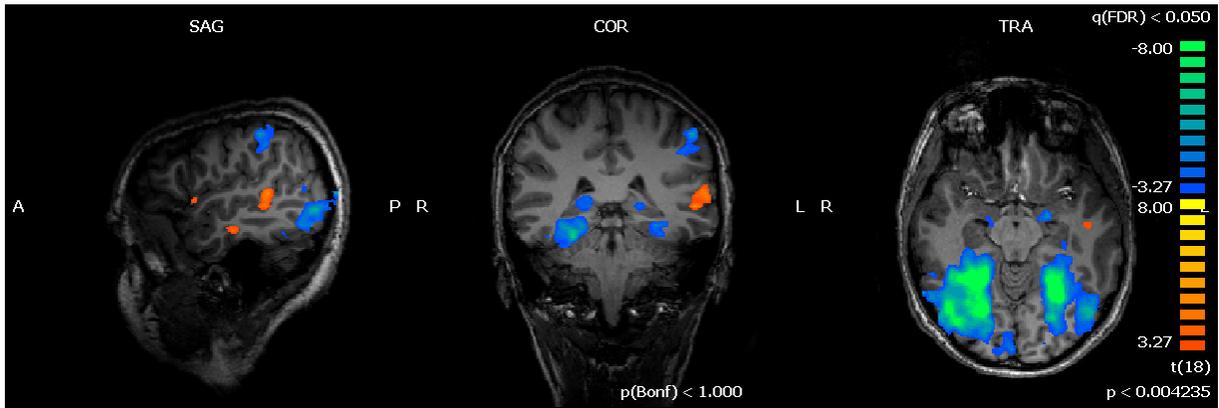
Statistical parametric maps of the t-contrast between Word *vs* Picture context thresholded at q(FDR) <0.05. Orange-yellow: areas responding to word context; blue-green: areas responding to picture context.

Figure 3.3 Differential activations between NR and DD induced by context
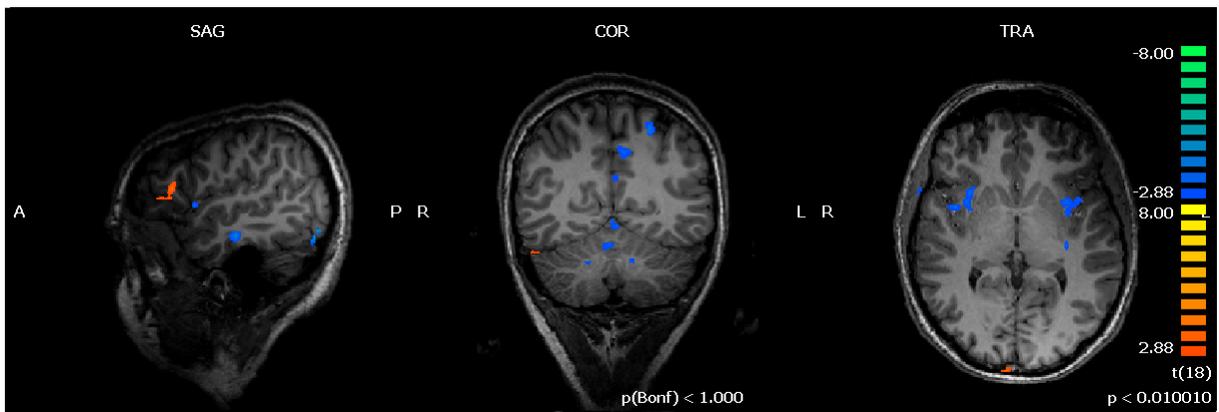
Statistical parametric map of the t-contrast NR(Word-Picture) > DD(Word-Picture) thresholded at p <0.01 uncorrected for multiple comparisons.

In NR, areas that showed increased activation during analogical reasoning task respect to semantic judgment were found in temporal, frontal and paralimbic regions, with a clear lateralization to the left hemisphere. In particular, in young NR analogical

reasoning evoked greater activations in the left fusiform gyrus (BA 37), in the posterior part of the left middle temporal gyrus (BA 22 and BA 39), in the left middle frontal gyrus (BA 6 and BA9) and in the left inferior frontal gyrus (BA 45 and BA 44) (See Figure 3.4.a and Table 3.6). In dyslexics the AnR task was associated with more localized foci of activation within the left hemisphere, involving also the posterior part of superior-middle temporal gyrus (BA22) and inferior frontal gyrus (BA45) (See Figure 3.4.b and Table 3.6).

Within the left hemisphere, significant differences between groups in analogical reasoning were found in fusiform gyrus (BA37), middle temporal gyrus (BA22), and inferior frontal gyrus (BA44), which were more active in NR respect to DD (See Table 3.7 and Figure 3.5).

No correlations were found in both groups between age, sex, RT and reading skills, and with the level of activity within areas found active during analogical reasoning.

Figure 3.4.a Areas activated during analogical reasoning in young normal readers
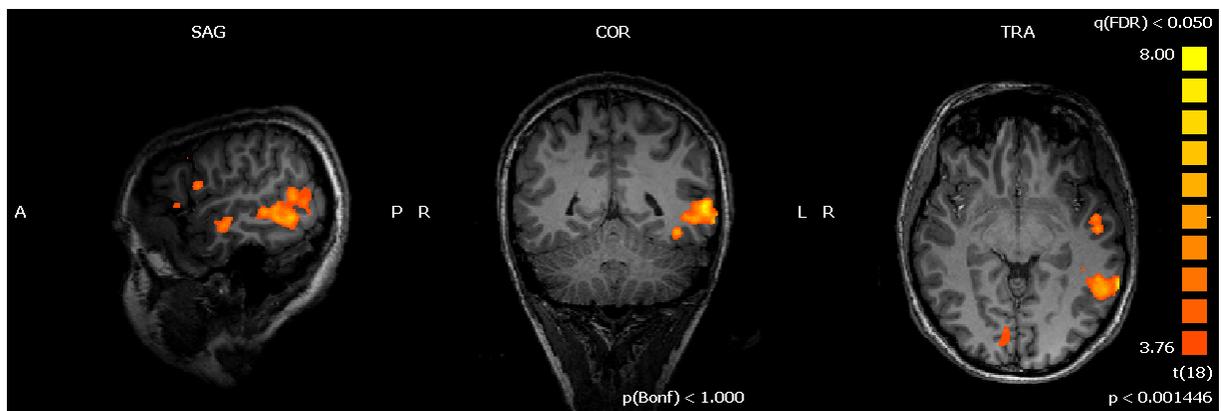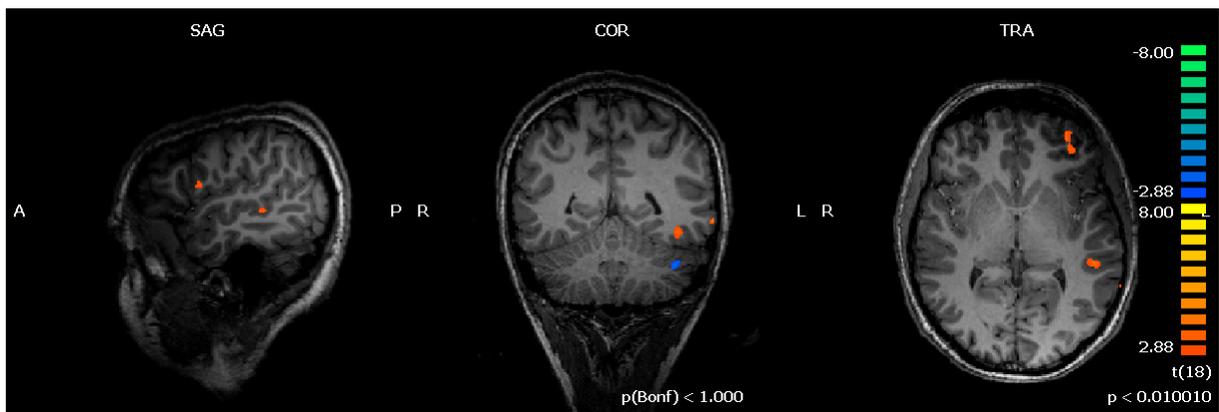

Statistical parametric maps of the t-contrast between AnR *vs* Sem Task displaying areas responding to analogical reasoning thresholded at q(FDR) <0.05.

Figure 3.4.b Areas activated during analogical reasoning in young dyslexics
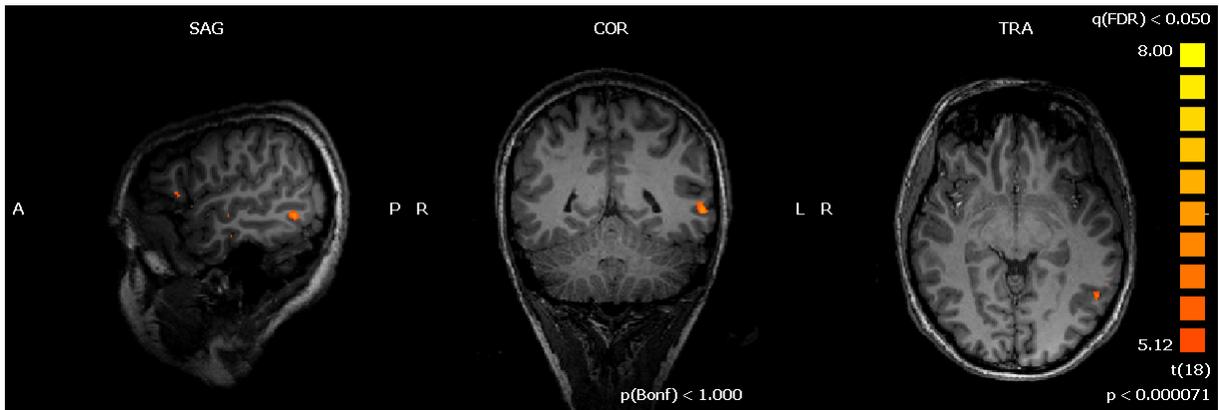
Statistical parametric maps of the t-contrast between AnR *vs* Sem Task displaying areas responding to analogical reasoning thresholded at q(FDR) <0.05.

Figure 3.5 Differential activations between NR and DD induced by analogical reasoning

Statistical parametric map of the t-contrast NR(AnR-Sem) > DD(AnR-Sem) thresholded at p <0.01 uncorrected for multiple comparisons.

In addition to whole brain analysis, we performed a ROI analysis in order to understand if the observed differences between normal readers and developmental dyslexics could be attributed to differences in the modality/strategy of analysis of the

material (pictures or words) in analogical reasoning. Among the areas that we found active for analogical reasoning, we focused on those involved in language and semantic processing as reported in the literature (Bookheimer, 2002; Chao, et al., 1999; Martin, 2007). Within these areas we selected two sets of clusters within the same Brodmann's areas that we found involved in AnR in the previous study: 1) areas involved in AnR where a significant differences between groups was found (BA44; BA22; BA37) and 2) areas activated in AnR which showed a functional overlap between the NR and DD (BA45, posterior portion of Middle-Superior Temporal Gyrus). The ROI analysis revealed distinct patterns of activity within these regions (mean beta values and sd are reported in the graphs in Figure 3.6).

In the left fusiform gyrus (BA37), both group showed greater activation to picture respect to words context (NR: p=0.0001; DD: p=0.01). NR showed also a task effect (p=0.0001) due to a higher involvement in Picture-AnR respect to Picture-Sem. On the contrary, the DD group did not show any effect related to the task.

The left BA22 was influenced by stimulus properties (context dependent response) in both groups, being more active in the word context (Words *vs* Picture: NR p=0.05; DD: p=0.004). In NR, BA22 showed also a greater response in analogical reasoning in both contexts (Word-AnR *vs* Word-Sem p= 0.005; Picture-AnR *vs* Picture-Sem p=0.001). Notably, in DD this area did not show any task effect neither in word nor in picture context (Word-AnR *vs* Word-Sem p= 0.18; Picture-AnR *vs* Picture-Sem p=0.15). Moreover, in DD it was active almost exclusively in the word context.

The inferior frontal gyrus (BA44) in NR showed a significant effect of context and task with greater involvement in words and in analogical reasoning (Word *vs* Picture p=

0.001; AnR *vs* Sem p =0.001). In DD the inferior frontal gyrus showed only an small effect for context (Word *vs* Picture p= 0.07), without any effect related to the task in both context.

The posterior middle/superior temporal gyrus (pMTG) showed a similar behaviour in both groups, with greater activation in analogical reasoning respect to the semantic task (AnR *vs* Sem: NR p< 0.0001; DD p< 0.0001) and without any context effect.

The BA45 was influenced by the type of task, showing greater activation for AnR in both groups (AnR *vs* Sem: NR p=0.002; DD p<0.0001). Its activity was not influenced by the context in dyslexics while it was more active for words in normal readers (Word *vs* Picture: NR p= 0.02; DD p=0.8).

Figure 3.6 ROI Analysis
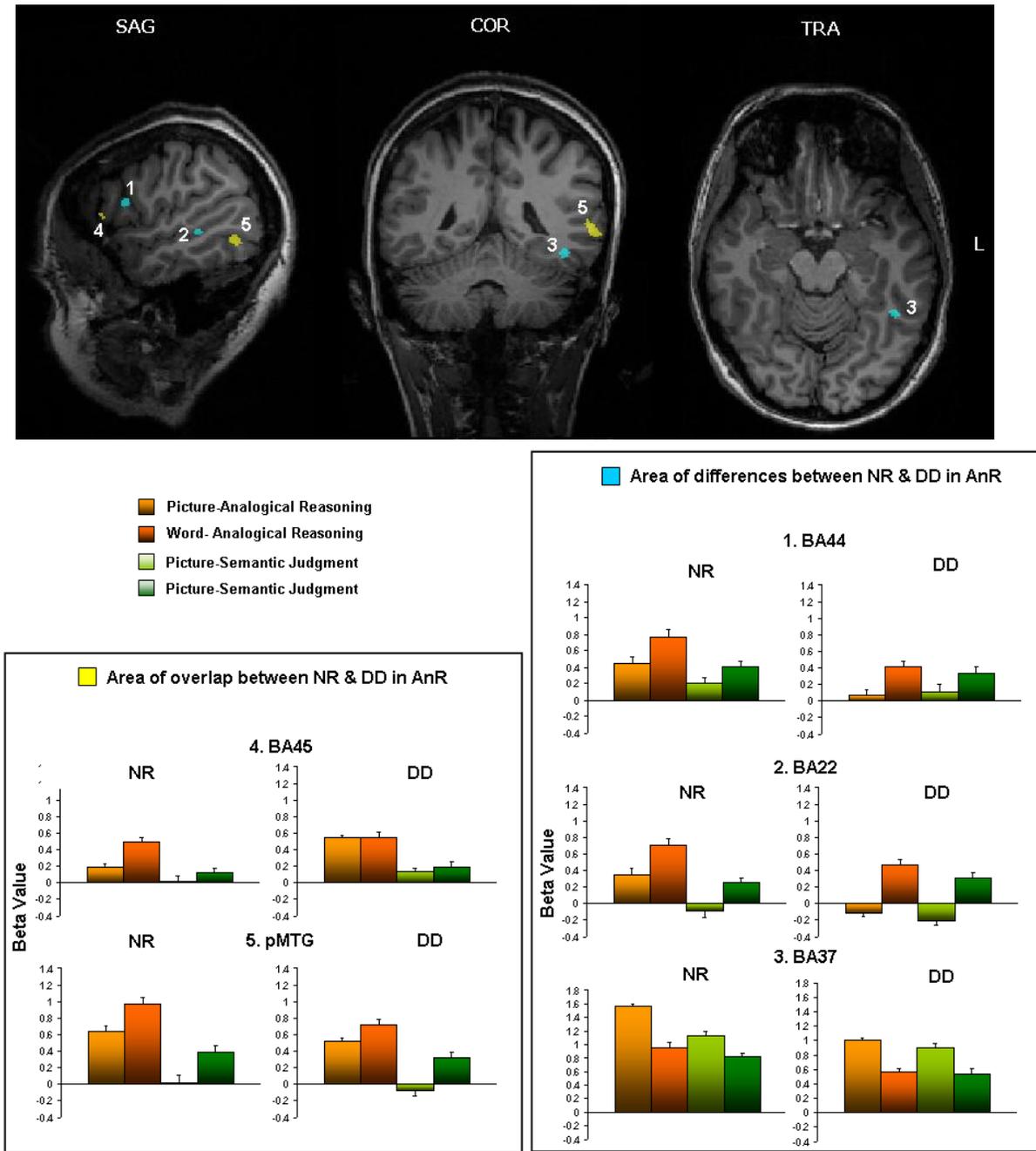
ROI analysis of the left hemisphere areas described in the results section. The plots depict the mean normalized beta values for the four conditions. Abbreviations: BA = Brodmann Area: pMTG = posterior part of Middle Temporal Gyrus.

Table 3.3 Context Effect in normal readers

Area	Talairach Coordinates			Nr of Voxels	BA
	x	y	z		
Picture *vs* Word					
R Cuneus	19	-95	5.3	306	18
R Precuneus	7.4	-58	42	124	7
R Fusiform Gyrus	33	-63	-0.98	36159	37/19
R Inf. Parietal Lobule	38	-38	36	215	40
R Middle Frontal Gyrus	41	31	18	103	46
R Amigdala	29	-3.5	-11	90	
R Cerebellum	20	-37	-41	165	
R Medial Frontal Gyrus	9.8	1.1	66	166	6/8
L Cuneus	-19	-76	34	298	19
L Precuneus	-5.6	-56	37	555	7
L Precuneus	-16	-61	48	817	27
L Post Cingulate	-17	-59	12	134	30
L Fusiform Gyrus	-45	-64	-9	19512	37
L Inf. Parietal Lobule	-49	-33	37	1171	40
L Claustro	-32	-10	-7.6	345	
L Cerebellum	-10	-66	-41	171	
Word *vs* Picture					
L Inferior Frontal Gyrus	-49	26	9.1	533	45
L Superior Temporal Gyrus	-55	-27	0.93	681	22
L ant Superior Temporal Gyrus	-60	-4.6	1.6	205	22

Table 3.4 Context Effect in dyslexics

Area	Talairach Coordinates			Nr of Voxels	BA
	x	y	z		
Picture *vs* Word					
R Lingual Gyrus	6.5	-88	-14	358	18
R Cuneus	21	-73	34	451	7
R Fusifoorm Gyrus	32	-64	-6.5	31417	37/19
R Thalamus	17	-31	2.4	145	
L Cuneus	-17	-94	6.3	308	17
L Inferior Temporal Gyrus	-32	-64	-7.9	13574	37/19
L Inf. Parietal Lobule	-31	-42	41	465	40
L Middle Frontal Gyrus	-34	23	44	544	8
L Middle Frontal Gyrus	-34	40	36	581	9
L Amigdala	-19	-6.4	-11	351	
Word *vs* Picture					
R Superior Temporal Gyrus	52	-25	6.1	247	
R Putamen	21	8.4	13	220	
L Middle Temporal Gyrus	-55	-37	4.9	1811	22
L ant Middle Temporal Gyrus	-46	-14	-12	490	21
L Precentral Gyrus	-46	-8	42	411	4
L Inferior Frontal Gyrus	-44	17	3.5	574	45
L Medial Frontal Gyrus	-3.5	-4.9	58	345	6
Cingulate gyrus	0.94	-26	29	400	
L Putamen	-14	3.3	9.1	236	

Table 3.5 Differences between NR and DD induced by context.

Area	Talairach Coordinates			Nr of Voxels	BA
	x	y	z		
NR (Word-Picture) *vs* **DD (Word-Picture)**					
R Parahippicampal Gyrus	18	-11	-23	268	28
L Middle Frontal Gyrus	-33	39	39	92	8
L Inferior Frontal Gyrus	-50	26	11	151	45
DD (Word-Picture) *vs* **NR (Word-Picture)**					
R Middle Frontal Gyrus	41	31	19	287	46
R Insula	40	3.3	-0.24	1401	13
R Inferior Frontal Gyrus	37	36	3.2	213	46
R Precentral Gyrus	36	19	38	213	9
R ant Cingulate	1.4	15	24	935	24
R ant Cingulate	0.28	37	25	227	32
L ant Cingulate	-7.7	25	23	500	
L Cingulate	-3.7	-5.6	33	341	24
L Precuneus	-7	-54	36	335	7
L Parietal lobe	-23	-52	53	234	7
L Insula	-34	0.74	-2.1	2017	13
L ant Middle Temporal Gyrus	-49	-16	-15	303	22
L Cerebellum	-19	-42	-26	1154	

Table 3.6 Analogical Reasoning Task in NR and DD.

		Talairach Coordinates				
	Area	x	y	z	Nr of Voxels	BA
AnR *vs* Sem						
	R Lingual Gyrus	7.5	-77	-4.9	933	18
	R ant Middle Temporal Gyrus	47	-7.4	-11	259	21
	R Precentral Gyrus	26	-11	49	312	6
Normal Readers	R Cerebellum	17	-71	-38	1121	
	L Precuneus	-3.2	-62	36	5100	7
	L Post Cingulate	-12	-57	12	530	30
	L Fusiform Gyrus	-40	-44	-13	739	37
	L post. Middle Temporal Gyrus	-46	-56	9.9	12262	39/22
	L ant Middle Temporal Gyrus	-47	-11	-11	1130	21
	L Middle Frontal Gyrus	-33	5	40	6534	6
	L Inferior Frontal Gyrus	-47	24	7.5	1062	45
	L Inferior Frontal Gyrus	-53	8.5	16	220	44
AnR *vs* Sem						
	R Precuneus	-0.23	-62	36	30	7
	L Precuneus	-30	-69	32	365	19
Dyslexics	L Parahippocampal Gyrus	-26	-38	-8.7	66	36
	L ant Middle Temporal Gyrus	-41	-0.12	-26	48	21
	L post Middle Temporal Gyrus	-55	-48	-1.3	409	22
	L Middle Frontal Gyrus	-30	-3.5	48	81	6
	L Inferior Frontal Gyrus	-51	19	8.9	48	45

Table 3.7 Differences between NR and DD induced by AnR

Area	Talairach Coordinates			Nr of Voxels	BA
	x	y	z		
NR(AnR-Sem) *vs* **DD(AnR-Sem)**					
R Inferior Frontal Gyrus	59	6.7	12	133	44
R Middle Temporal Gyrus	54	-32	-3.2	88	21
R Fusiform Gyrus	54	-41	-21	91	20
R Insula	43	-30	-4.6	123	22
R Precuneus	14	-75	46	137	7
R Cerbellum	27	-68	-41	431	
L Fusiform Gyrus	-41	-44	-13	94	37
L Middle Temporal Gyrus	-48	-34	0.31	97	22
L Inferior Frontal Gyrus	-52	7.1	17	85	44
L Middle Frontal Gyrus	-32	48	1.3	92	10
DD(AnR-Sem) *vs* **NR(AnR-Sem)**					
R Medial Frontal Gyrus	7	58	20	333	10
L ant Middle Temporal Gyrus	-41	-0.83	-27	121	21
L Cerbellum	-39	-45	-35	133	

Discussion

The aim of the present study was to investigate the higher cognitive functions, in particular the analogical reasoning, in a young population of dyslexics in order to understand if the reasoning may be considered a talent within this population and the reading disorder may influence the reasoning in relation to the language load requested by the stimulus format.

The hypothesis was that, if a particular talent is present in dyslexics, they may have shown significant brain reorganization compared to normal readers, especially when reasoning on pictures, which allow but do not require a mandatory use of language.

The neuropsychological investigation

The neuropsychological assessment confirmed the reading impairment in the dyslexics both in terms of speed and accuracy, but with a sparing of comprehension. In addition, with the limit due to the numerosity of the controls, the performance between normal readers and dyslexics diverges in two main cognitive domains: verbal language abilities and working memory. While the overall language domain of dyslexics remains within the normal range, a clear impairment is present for the working memory functions. These findings are in agreement with the current literature on dyslexia across different cultures and languages (De Clercq-Quaegebeur et al., 2010; Everatt, Weeks, & Brooks, 2008; Smith-Spark & Fisk, 2007): in particular, working memory deficits have been described as one of the major characteristics of developmental dyslexia and

independently form age and has been linked to the deficit in the automatization of reading (Altemeier, Abbott, & Berninger, 2008; Bacon, et al., 2007; Reiter, et al., 2005; Smith-Spark & Fisk, 2007). In our dyslexic group the working memory deficit is confined to verbal-auditory modality confirming the deficit in the phonological loop; instead, visuo-spatial working memory (Visual Sequencing Memory and Memory for Location subtests of TOMAL) are in the higher normal limit, suggesting a possible dissociation between domains within working memory. On the other hand, in our sample we found impairment on Coding subtest of WISC scale: it is a non verbal task which requires, in addition to working memory components, also automatization and rapid automatic learning, that have been indicated as weak functions in dyslexia (Altemeier, et al., 2008; Nicolson & Fawcett, 1990; Smith-Spark & Fisk, 2007).

Although the dyslexics produced a lower score in language-related abilities and in some executive functions, their performance in most of non-verbal tasks was as good as controls, supporting the idea that dyslexia may be linked to a talent in the non-verbal domain that partly compensates the language difficulties (Bacon & Handley, 2010; Miles, 1993).

In most of problem solving tasks (WCST; Block Design, Maze), dyslexics performed slightly better than normal readers, in agreement with some literature data (De Clercq-Quaegebeur, et al., 2010; Everatt, et al., 2008; Reiter, et al., 2005). Our results in executive functions partially overlap with those found by Reiter and colleagues in an extensive study on executive functions in dyslexic children. Reiter (2005) documented an impairment in working memory, inhibition and rapid shifting processing. But in problem solving tasks their dyslexic children performed equally or better respect to the controls: in

the WCST dyslexics tended to perform better than non-dyslexics, making fewer mistakes and perseverations and matching more cards with regard to the rule. In the same study, dyslexics and controls did not differ on Tower of London test concerning the number of problems solved in minimal number of moves. The difference was confined to the increased planning time of dyslexics. Nevertheless, the Authors interpreted the WCST performance by the fact that children with dyslexia were familiar with the psychometric assessment while non-dyslexic were not, and they focused the attention on the deficit in working memory, shifting and inhibition suggesting a general impairment of executive functions in dyslexia.

Considering our data, we suggest a possible dissociation within the executive functions with a distinction of executive functions such as working memory, rapid automatic shifting, automatization, which are impaired in dyslexics, from others executives functions i.e. planning and problem solving.

In our sample, the problem solving and the non-verbal domain may be considered a relative strength of dyslexics, in particular if compared to their weakness in the manipulation of verbal material and to the impairment in reading and working memory. In addition, despite the deficit in reading speed and accuracy, the reading comprehension is relatively spared. It has been documented that the performance in some executive abilities (rapid automatic shifting, automatization and inhibition) predicts the reading outcome in terms of accurate decoding and automatization of reading but not in terms of text comprehension (Altemeier, et al., 2008). Our results indirectly sustain these findings. One possibility is that different kind of executive functions support different aspect of reading: working-memory, rapid automatic shifting, automatization and inhibition

contribute to grapheme-phoneme conversion, while comprehension may require planning and problem solving abilities (Altemeier, et al., 2008; Altemeier, Jones, Abbott, & Berninger, 2006).

In summary, the results of the neuropsychological evaluation support the idea that dyslexia is a complex disorder characterized not only by areas of weakness but also from cognitive strengths represented by problem solving and abilities within the non-verbal domains.

The major limit of this study was the limited number of participants in particular in the control group, thus the data need to be confirmed through further investigations on larger groups, extending the study to younger children and adding specific tasks for the assessing of inhibition and shifting.

If these results will be confirmed, at least in term of relative talent of dyslexia, they may have implications in the rehabilitation and teaching strategies.

The fMRI investigation

The main interest of the fMRI study was to explore the differences in analogical reasoning between young dyslexics and normal readers using two stimuli format (picture and words) which required different load on language components. The analysis of neural activity and the functional modulation of areas involved in analogical reasoning in relation to the stimulus format (pictures and words) were used to infer if the context induces different strategies to solve the analogy. In the introduction we hypothesized that since in our task picture naming and the associated lexical-phonological analysis is not mandatory, dyslexics may have used different strategies which may be correlated

with a different involvement of brain areas related to reasoning itself compared to the normal readers.

Regardless of the task, in the word context both groups of young subjects activated a left lateralized network, including areas indicated by the literature as core for language processing and very close to the pattern of activity we found in adults. Also the picture context was associated in both groups with similar patterns of activation involving a large set of posterior occipito-temporo-parietal regions, as in adults. The differences respect to the context, independently from the task, between normal readers and dyslexics are limited to the inferior frontal gyrus which is less engaged in dyslexics in the word context. The activity in the inferior frontal gyrus has been linked to the improving of reading skills during development and in particular with the phonological awareness and phonological naming (Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003), thus the differences we found here may be due to differences in the reading skill between the two groups. On the same track, the engagement of insula by dyslexics in word context may be due to the relative unfamiliarity with words. In fact, it has been suggested that increased activation of the insula reflects greater demands on articulatory speech plans when unfamiliar stimuli versus familiar are presented, independently from the request of overt or covert speech (Price, 2010).

Regarding the main interest of the study, the results on young participants confirm that the left hemisphere plays a central role in relational reasoning since early adolescence. In fact, in young unimpaired readers analogical reasoning evoked a greater activity in a clearly left lateralized circuit including the fusiform gyrus, the parahippocampal region, the posterior part of the superior temporal gyrus, the middle

and inferior frontal gyri. These activations confirm the results of the previous study on adult participants and are consistent with the neuroimaging literature (Bunge, et al., 2005; Geake & Hansen, 2005; Goel & Dolan, 2004; Kroger, et al., 2002; Luo, et al., 2003; Wendelken, et al., 2008; Wharton, et al., 2000). However, differently form the adult group, during analogical reasoning the young normal readers engaged also the Broca's area, suggesting that solving an analogy induces a greater phonological demand at this age.

Also in dyslexics the left hemisphere appears to be dominant for analogical reasoning with involvement of language-related areas. Referring to the hypothesis formulated in the introduction, this finding excludes that reading impairment induces a deep brain reorganization and/or the recruitment of a compensatory system, nor it is linked to the persistence of a less lateralized pattern typical of early and middle infancy (Moses, et al., 2002). Thus, it seems more likely that reading disability induces more subtle brain reorganization. In fact, differently from normal readers, dyslexics are associated with a more localized but globally weaker activation limited to the left posterior middle temporal gyrus and frontal cortex. These findings are in agreement with the current neuroimaging literature on dyslexia which reported that the reading impairment is associated with a hypoactivation within the left hemisphere relatively independent from the task, stimulus format-modality and age (Booth, Bebko, Burman, & Bitan, 2007; B. A. Shaywitz et al., 2002; S. E. Shaywitz & Shaywitz, 2003). The weaker activation in dyslexics' brain respect to control has been considered as a sort of signature of dyslexia and it has been interpreted as the functional counterpart of a specific neural abnormality (McCrory, Mechelli, Frith, & Price, 2005; B. A. Shaywitz, Lyon, & Shaywitz, 2006). On the other hand, we have to take into account the possibility that the reduction of activity reflects an

increased efficiency in terms of more focal and more specialized brain activations (Wartenburger, Heekeren, Preusse, Kramer, & van der Meer, 2009). In other words, the decreased brain activity may be attributed to a more specific/efficient neural circuit activated during analogical reasoning. This possible interpretation is partially supported by the behavioural data acquired during scanning which did not reveal any interaction between group and accuracy in analogical reasoning task. Our data seem to indicate that dyslexics can efficiently perform analogical reasoning with reduced allocation of brain resources involving the anterior part of inferior frontal gyrus and posterior middle-superior temporal gyrus. These two regions, which are active also in young normal readers, overlap with those found to be critical in adult participants for reasoning confirming the critical role of inferior frontal gyrus (BA45) and pMTG for reasoning itself. Despite the common response during analogical reasoning, the functional behaviour of these two regions partially diverges between groups. The pMTG showed a similar functional modulation in relation to task and context in both groups: its activity was higher in word context, but it displayed an additional modulation being significantly more active during analogical reasoning independently from the context. Although part of the pMTG response has been linked to the phonological access (Graves, et al., 2008), and the higher activity in word context support this role, the associated activity also in picture analogical reasoning (but not in semantic judgment) in both groups strongly suggests that this area specifically contributes to reasoning at least in adolescence. In fact, in the first study the activity of the posterior part of superior temporal gyrus during reasoning was limited to word context. From a developmental point of view, the frontal cortical maturation and white matter myelination/organization continues from childhood

to young adulthood (Qiu, Tan, Zhou, & Khong, 2008), and these structural modifications have been linked to the development and improvement of the complex executive functions underlined by frontal regions. Within this scenario, it might be supposed that pMTG and adjacent regions, which are involved in integration and cross-modal binding (Beauchamp, Argall, Bodurka, Duyn, & Martin, 2004; Hein & Knight, 2008; Hocking & Price, 2008), support reasoning especially in the early age, when the maturation of neural substrates of higher cognitive function is not completed yet. The importance of the integrative role of this region comes also from the observation that in dyslexic children the pMTG is indicated as part of the compensatory system which underlines their skilled reading abilities (B. A. Shaywitz et al., 2004).

Differently from pMTG, the inferior frontal gyrus (BA45) showed a different modulation between the two groups. If the pattern of activity on young controls is similar to those found in adults, in dyslexics the load of the anterior part of inferior frontal gyrus in analogical reasoning is not influenced by the context showing exactly the same load during picture and word reasoning. Thus, it seems that dyslexics reason on the material independently from the features, and they rely more on the functions underlined by BA45. The anterior part of IFG plays a role in the selection of task-relevant knowledge amidst competing irrelevant knowledge (Kimberg & Farah, 1993; Thompson-Schill, et al., 1997; Wagner, et al., 2001) and it has been suggested that it serves to activate, enhance and/or maintain the activation state of semantic representations that reside in posterior cortical areas (Wendelken, et al., 2008). According to this model, the role of inferior frontal gyrus in reasoning is to influence the activation state of semantic representations: it could facilitate the relational retrieval or the integration of relations and items to solve the

analogy. In this view, it may be suggested that dyslexics need higher top-down control provided by BA45 during the analogical reasoning independently form the context. An alternative explanation for the observed pattern of activation of BA45 in dyslexics is that the selection between competing informations/relations required additional activation due to the weak working memory skills and automatization process documented in the neuropsychological evaluation of these patients, which agrees with what is reported in the literature on dyslexia (Altemeier, et al., 2008; Nicolson & Fawcett, 1990; Smith-Spark & Fisk, 2007). It has been proposed that dyslexics employ strategies of "conscious compensation" to hide their difficult in automatization allocating more resources to the task in which they are involved (Nicolson & Fawcett, 1990). In this scenario, the high load of BA45 during reasoning independently from the context may represent a strategy of compensation.

The main differences in analogical reasoning between dyslexics and normal readers were found in language core areas and in the left fusiform gyrus which is linked to conceptual knowledge access: young normal readers respect to dyslexics evoked an increased activity in all of these regions. This result is in agreement with the current literature of dyslexia, which indicates that differential activations between dyslexics and normal readers are clustered in three left regions: inferior frontal gyrus, temporal lobe (Wernicke's area), and occipito-temporal region (McCrory, et al., 2005; B. A. Shaywitz, et al., 2006).

The functional behaviour of these areas revealed that only the normal readers rely on the activation of BA44 and BA22 in both context, while the dyslexics engaged the two language areas almost only when reasoning had to be performed within the word context,

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with limited/absent activation during reasoning on pictures. Moreover, differently from normal readers, within word context none of these regions showed a modulation related to the task in dyslexics. Thus, this different pattern of activity between groups suggests that the two groups adopted different modalities of analysis: young normal readers rely on the lexical-phonological processing underpinned by these areas (Graves, et al., 2008; Heim, et al., 2008) to solve reasoning in both context, while dyslexics required it only when the context forced the use of a verbal strategy, such as in the word context. Notably, it seems that only young dyslexics displayed a pattern of analysis similar to that of adults, where the activity of these areas was limited to reasoning in word context.

Differently from the BA44 and BA22, the left fusiform gyrus is recruited in both groups with a similar pattern of activation even if in dyslexics this area was less active respect to controls in both contexts. This is in line with the neuroimaging literature which indicates that the differences between dyslexics and normal readers in the occipito-temporal region are the most consistent finding using orthographic stimuli and they have been interpreted as an expression of the impaired phonological processing in dyslexia (Brunswick, McCrory, Price, Frith, & Frith, 1999; Paulesu et al., 2001; B. A. Shaywitz, et al., 2002). A similar hypoactivation in the left occipito-temporal area of dyslexics (x = −48, y = −54, z = −16, thus more posterior and inferior respect our region) has been documented also for picture naming tasks and it as been interpreted as the functional counterpart of a more general impairment in retrieving phonology from visual input (McCrory, et al., 2005). Nevertheless, other studies failed to confirm these differences in picture processing between dyslexics and normal readers within the left occipito-temporal region (Grande, Meffert, Huber, Amunts, & Heim, 2011; Trauzettel-Klosinski, et al., 2006). Despite it is

possible that occipito-temporal regions are involved in the integration of visual, phonological and semantic information (Price & Devlin, 2003), our data does not allow to formulate an hypothesis on the role played by occipito-temporal cortex-fusiform gyrus in reading disorders: overall our results seem to indicate that the critical differences in reasoning between dyslexics and controls are not linked to the occipito-temporal region and that, despite the reading disability, the semantic system can be accessed independently from the stimulus properties.

In summary, our study confirms the critical role of the inferior frontal gyrus (BA45) in analogical reasoning on semantic material and suggests a potential developmental trajectory of the role of posterior part of middle temporal gyrus in reasoning.

The present data support the hypothesis that in analogical reasoning dyslexics and normal readers rely on different strategies of analysis which have their neural counterpart not only in a more localized activation but also in a different recruitment-modulation of some brain regions. Most importantly, the reading disorder did not affect the efficiency of reasoning on pictorial material: we hypothesize that if the task does not require a mandatory lexical-phonological access, dyslexics just avoid the use of core language areas that may not be critical to solve the analogy. Instead, young normal readers activated BA44 and BA22 not only in the word but also in the picture context, suggesting that, if verbal resources are available, they tend to use them even if they may be not critical to solve the task

Overall the data confirm the hypothesis that analogical reasoning may be performed without the involvement of lexical-phonological components, a strategy that can be used

by adults if needed and is a modality of reasoning that young dyslexics may use to bypass their language impairment.

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Chapter IV

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Brain activity during analogical reasoning within non-verbal context

The results of the previous study on pictures and words were not exhaustive respect to the influence of context/stimuli format on the analogical reasoning network. Thus, a new fMRI design was implemented where analogical reasoning was performed either on meaningful or on abstract geometrical pictures.

The aims of this study were:

1) To confirm the data obtained during reasoning in the picture context with a better control on the influence by semantic contents of the stimuli: in the previous study the semantic judgment was composed by three pictures, here the semantic judgment was more similar to the analogy task, and had to be performed on two pairs of stimuli;

2) To explore the influence of a semantic-free context on the network found active in reasoning. We used geometrical abstract figures to avoid the semantic content and expected that the dorsolateral prefrontal cortex confirmed its context-independent activity. Regarding the behaviour of the anterior part of inferior frontal gyrus (BA45), if its role was linked to the analogical reasoning itself, we expected its involvement also when abstract stimuli had to be manipulated. Conversely, if the key role of BA45 was related

only to manipulation of semantic knowledge to reasoning, but only when semantic knowledge, we expected it to be silent during reasoning within the abstract context;

3) To further explore the possible role of verbal language in reasoning. In the first study we suggested that visual information conveyed by pictures of concrete items is sufficient to perform an analogy without passing through any verbal label. In the present study we asked subject to reason on non-nameable stimuli to verify if language was engaged to create   linguistically shaped relations (Gentner, Holyoak, & Kokinov, 2001).

Material and Methods

Subjects

13 right-handed subjects were recruited for this study (5 males and 8 females, mean age 33 years, range 22-51). All participants were Italian native speakers with no history of neurological or psychiatric disorders. Handedness was assessed using the Edinburgh Inventory (Oldfield, 1971).

Three subjects were excluded form the analysis because they gave less than 70% of correct responses in at least one of the task proposed.

The study was approved by the Ethics Committee of the University of Trento and all participants signed an informed consent form.

Stimuli and task

We prepared 32 stimuli (21 true and 11 false) for each task and context (Picture and Abstract): the analogical reasoning (AnR), the categorization (Cat) and visual search (VS).

In the Picture context, each stimulus was composed by two pairs of grey scale pictures. In the Picture-AnR task, subjects were asked to verify whether the relationship between the two items of the first pair corresponded to the relationship between the items of the second pair (Figure 4.1.a). The participant was warned that a relationship was always present within each pair of pictures but it could be either the same or different between the pairs.

In the Picture-Cat task, the subject had to verify if the pictures of each pair belonged to the same semantic category: if both pairs defined a category, the response was true, otherwise (i.e. one of the pairs did not define a category) the response was false (Figure 4.1.b). To avoid the possibility that the correct response could be given analyzing only one of the pairs, we instructed the subject that the response was true also if none of the pairs defined a semantic category. To simplify the task, we explained the subject that whenever both pairs were homogeneous respect to defining/not defining a semantic category, the response was true.

In the Abstract context, each stimulus was composed by two pairs of line drawing geometrical non-nameable pictures. Each picture was composed by two geometrical abstract shapes arranged according to three predefined categories: overlapping, separated and inserted (see Figure 4.2).

In the Abstract-AnR task, within each pair the same couple of shapes were depicted always arranged according to the same category but spatially rotated or modified in their

reciprocal position (see Figure 4.2.a). The subject was asked to verify whether the pictures in one the pair underwent the same type of transformation of the other pair.

In the Abstract-Cat task, the two couple of shapes within each pair were always different and the subject had to verify if they were arranged so that they belonged to the same predefined category (i.e. overlapping, separated or inserted): if both pairs defined a category the response was true, otherwise (i.e. one of the pair did not define a category) the response was false (see Figure 4.2.b). The category defined by one pair was always different from the other one. As for the Picture-Cat task, to avoid the possibility that the correct response could be given analyzing only one of the pairs we instructed the subject that the response was true also if none of the pairs defined a homogeneous category.
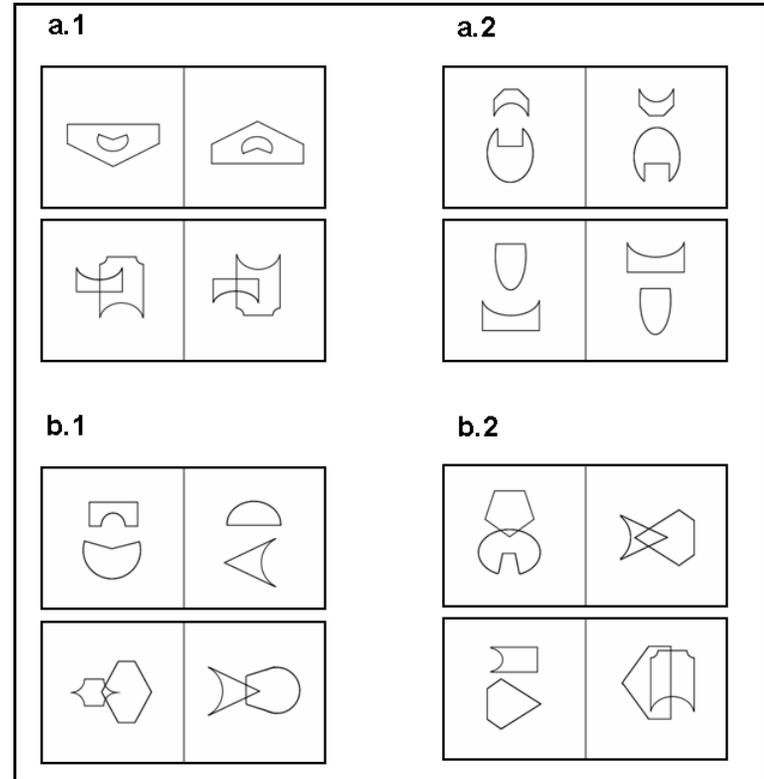
Figure 4.3 show the examples of stimuli used for the VS task. For this task the subject had to search in each pairs the target (white square) among six distractors (white triangles) and verify if it was present or not in both pairs.

Figure 4.1 Examples of stimuli used in Picture context

**Figure 4.2 Examples of stimuli used in Abstract context**
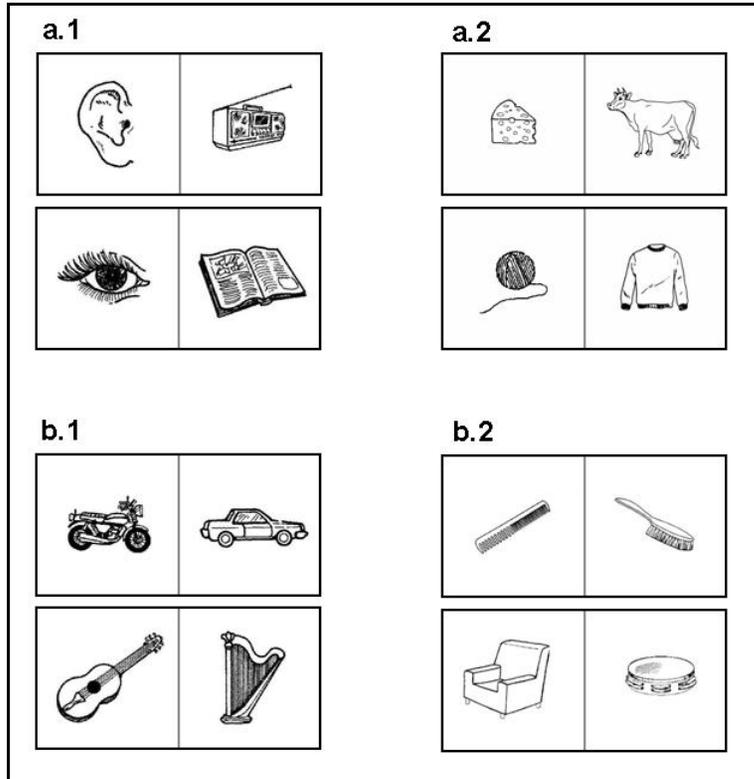
(a.1) Example of True item of Picture-AnR; (a.2) Example of False item of Picture-AnR;
(b.1) Example of True item of Picture-Cat; (b.2) Example of False item of Picture-Cat.

(a.1) Example of True item of Abstract-AnR; (a.2) Example of False item of Abstract-AnR;
(b.1) Example of True item of Abstract-Cat; (b.2) Example of False item of Abstract-Cat.

Figure 4.3 Examples of stimuli used in the Visual Search task
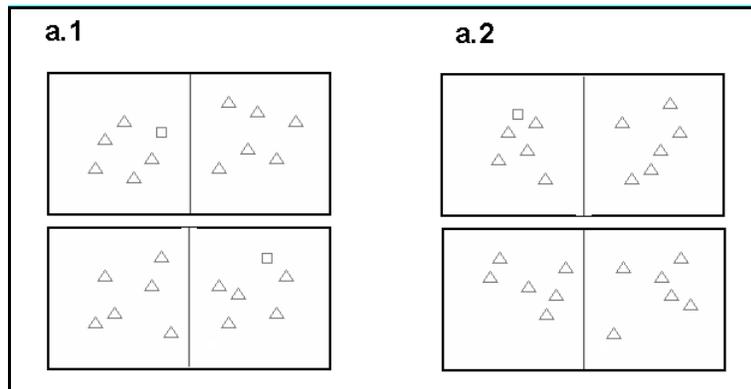
(a.1) Example of True item; (a.2) Example of False item.

fMRI design and procedure

We implemented a design where analogical reasoning was performed either on two pairs of grey scale pictures (picture context) or on two pairs of abstract geometrical stimuli (abstract context). Two categorization judgment tasks, one for each contexts, and a visual search task were used as control conditions to allow a statistical analysis factoring out visual perception, eye movements, and motor response form the analogy tasks.

The presentation of the stimuli was performed using a block fMRI design with one run for each context (Picture and Abstract). Each run contained 24 blocks, eight for each task (AnR, Cat, VS) presented alternately. Each block contained four stimuli and it was preceded by specific instructions for task and context (2 s). On all tasks, participants viewed the two pairs of stimuli previously described displayed

simultaneously on the screen and they were required to make a yes/no response only while stimuli were visible on the screen by pressing with their right hand one of two buttons of a response pad.

The minimum and maximum stimulus durations were 500 and 5500 ms respectively. For response times faster than 500 ms, the stimulus disappeared immediately after the minimum duration. Otherwise, the stimulus disappeared as soon as the subject gave the response or, in case no response was given, after the maximum duration. The next stimulus was presented after a blank screen lasting 500 ms.

The resulting maximum block duration was 24 s. A variable additional period of visual fixation was added after the last stimulus of the block to compensate for responses shorter than 5500 ms and control for the block onset time. A fixation cross lasting between 8 and 12 s was presented between blocks. At the beginning and at the end of the runs a fixation cross was presented for 17.6 s and 17.2 s respectively. The total duration of each run was 15 min and 21 s.

Before starting the experiment subjects underwent a training session outside the scanner with 4 additional blocks for each task in order to familiarize with the experiment.

Imaging data acquisition

Brain images were collected with a 4-Tesla Bruker MedSpec scanner (Bruker Inc., Ettlingen, Germany) using an 8-channel head coil. During the scanning sessions, the motor response was collected using a fiber-optic two button response pad (Cedrus, San

Pedro, Ca, USA). The stimuli were back projected at the center of the visual field on an acrylic screen viewed by the subject through a mirror attached to the head coil using E-Prime software (Psychological Software Tools, Pittsburgh, PA, USA).

Functional images were acquired using a T2*-weighted gradient-echo echo-planar sequence (repetition time = 2200 ms, echo time = 33 ms, flip angle = 75°, acquisition matrix = 64 x 64, slice thickness = 3 mm, inter-slice gap = 0.45 mm, field of view = 192 x 192 mm, number of slices = 37). Each functional run had 404 brain volumes; at the beginning of each run five dummy scans were acquired.

For the subsequent superimposition of functional statistical parametric maps, a high-resolution structural 3D T1-weighted image was acquired (MPRAGE sequence, resolution 1x1x1 mm^3, acquisition matrix 256 x 224; number of slices = 176; repetition time = 2700 ms, echo time = 4.18 ms, inversion time = 1020 ms).

Imaging data analysis

Preprocessing and data analysis were conducted using BrainVoyager QX 1.9 software package (Brain Innovation, Maastricht, The Netherlands).

Functional images from each subject were corrected for slice time acquisition with cubic spline interpolation. All volumes were realigned using a 3D rigid-body spatial transformation to the first volume of the first functional run. Temporal filtering included linear trend removal and a 0.028-Hz (5 cycles in time course) high pass filter to eliminate low frequency noise. The functional data were co-registered to structural images and they were spatially smoothed using a Gaussian kernel (full width at half maximum = 4 mm) and resampled to 2x2x2-mm^3 cubic voxels. The structural and co-

registered functional data were normalized into standard stereotaxic space (Talairach & Tournoux, 1988). Statistical analysis was performed using a multi-subject general linear model random effect analysis in BrainVoyager QX 1.9 software.

A regressor for each set of the types of trials (Picture-AnR, Abstract-AnR, Picture-Cat, Abstract-Cat and VS) was created for each functional run and convolved with a standard hemodynamic response function. Scans acquired during visual fixation were considered as baseline. The regressors of all subjects were used to implement two multi-subject GLM random effect analysis separate for Abstract and Picture run. Z-transformation was used for normalization of signal respect to the baseline. Six motion regressors (3 translation and 3 rotation parameters) on x, y, z axes were included in the analysis as covariates of no-interest. The reaction time was added as covariates to exclude that the activations can be due to the response time differences. Beta maps were generated for each subject for each of the following contrast: Picture *vs* Abstract; AnR *vs* Cat; Picture-AnR *vs* Picture-Cat, Abstract-AnR *vs* Abstract-Cat, Picture-AnR *vs* Abstract-AnR; Picture-AnR *vs* VS; Abstract-AnR *vs* VS. The beta maps of each subject for each contrast of interest obtained from the GLM analysis were entered into ANOVA design to explore the influence of task and context.

The resulting statistical parametric maps were corrected for multiple comparisons using the false discovery rate (FDR) approach with at least $q<0.05$ and excluding all clusters extending less than 0.2 cubic centimeters. The sets of clusters of voxels found to be significantly activated after this statistical correction were used to define regions of interest (ROI) on which to perform post-hoc t-tests.

The Talairach Client software (Lancaster, et al., 2000) was used to assign Talairach Atlas labels for a given x,y,z coordinate, represented by the center of gravity of each cluster of activation.

Results

Behavioral in-scanner results

Mean accuracy was 86% and 93% for the analogical reasoning (AnR) and categorization (Cat) tasks respectively (Picture-AnR: mean 88%, sd 10%; Abstract-AnR: mean 83%, sd 7%; Picture-Cat: mean 91%, sd 4%; Abstract-Cat: mean 95%, sd 4%). The mean accuracy in VS task was 97% (sd 4%) in both runs. In abstract context the mean accuracy was 89.2% (sd 8%); in Picture context accuracy was 89.9% (sd 8%).

The ANOVA for repeated measures revealed that accuracy was significantly higher in Cat task respect to AnR ($F[1,9] = 21.39$; $p=0.001$). No effect for context was found ($F[1,9] = 0.27$; $p=0.6$) and an interaction between task and context was present ($F[1,9] = 7.28$; $p=0.02$).

Mean response time (RT) was 3041 msec and 2402 msec for the AnR and Cat tasks respectively (P-AnR: mean 2580 ± 603 msec; Abstract-AnR: mean 3502 ± 235 msec; Picture-Cat: mean 2297 ± 380 msec; Abstract-Cat: mean 2508 ± 292 msec). The mean RT in VS task was 1313 ± 329 msec. In abstract context the mean RT was 3005 msec (± 571 msec); in Picture context the mean RT was 2439 msec (± 512 msec).

The ANOVA for repeated measures revealed that the RT in Cat tasks was significantly faster than in AnR tasks ($F[1,9] = 169.06$; $p<0.00001$). A significant effect of

context was present with faster RTs for pictures (F[1,9] = 20.76; p=0.001). A interaction was found between task and context (F[1,9] = 9.12; p=0.01).

fMRI results

The fMRI results are summarized in the tables at the end of the results section.

The context effect reveals a clear distinct pattern between Picture and Abstract context. Compared to abstract context, the Picture context was associated with a bilateral greater activation of the fusiform gyrus and left hemisphere activations in the middle temporal gyrus and in the middle and inferior frontal gyrus (comprising the BA 45, 46, 47). The Abstract context respect the Picture was associated with a right lateralized pattern with greater activation in the bilateral parietal lobe, more extended in the right side, and the right precentral gyrus involving also the inferior frontal gyrus (Table 4.1 and Figure 4.4).

Fig 4.4 Context Effect
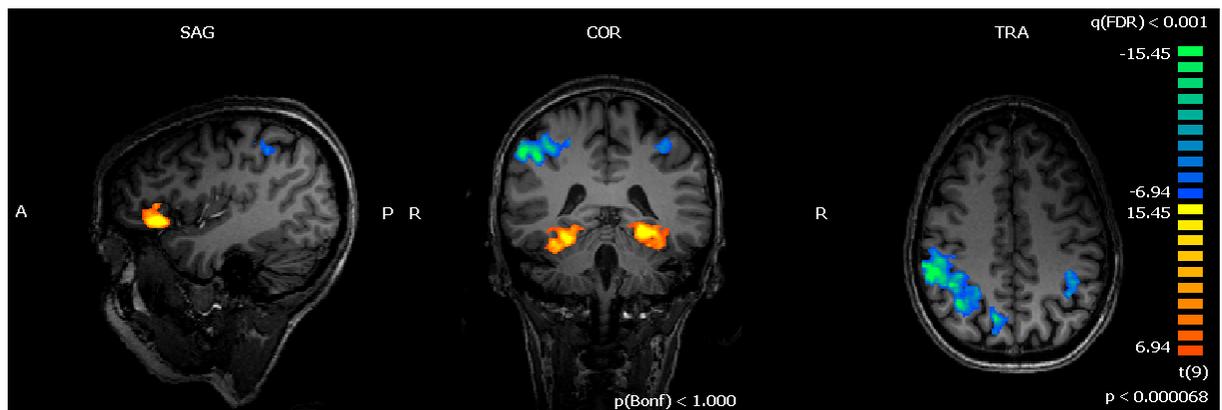
Statistical parametric map of the t-contrast between Picture *vs* Abstract context thresholded at q(FDR) <0.001. Orange-yellow: areas responding to Picture context; blue-green: areas responding to Abstract context.
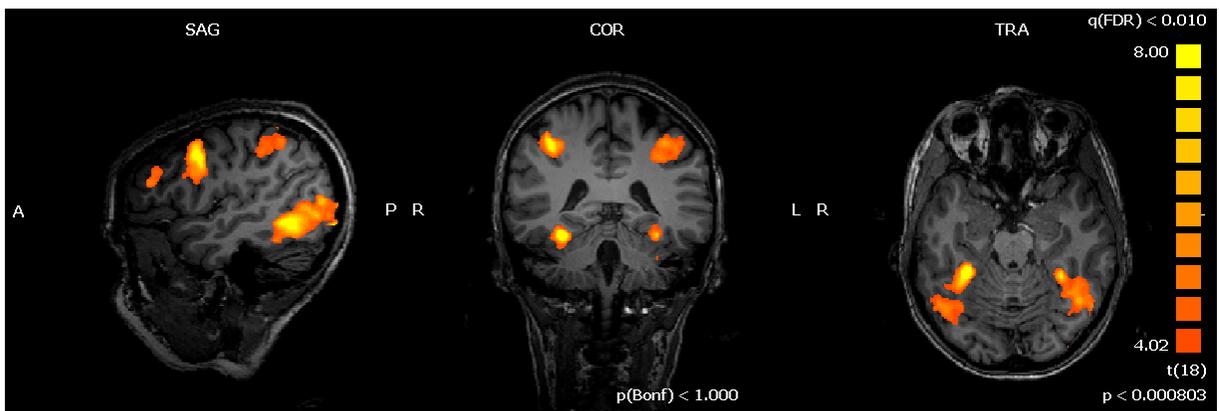
The analogical reasoning task respect to the VS was associated with strong engagement of the associative visual areas, the frontal and prefrontal cortices in both contexts. The Abstract-AnR also evoked bilateral activation of superior parietal lobe. Within the frontal cortex, the Picture AnR engaged BA45, 46, 47 (Figure 4.5 and Table 4.2).

Fig.4.5 Analogical reasoning *vs* Visual Search

a. Picture-AnR *vs* VS
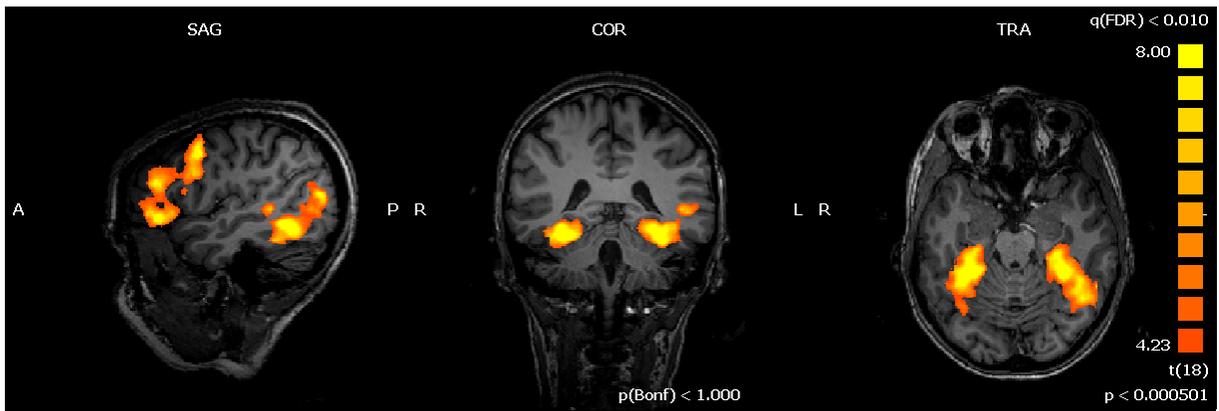
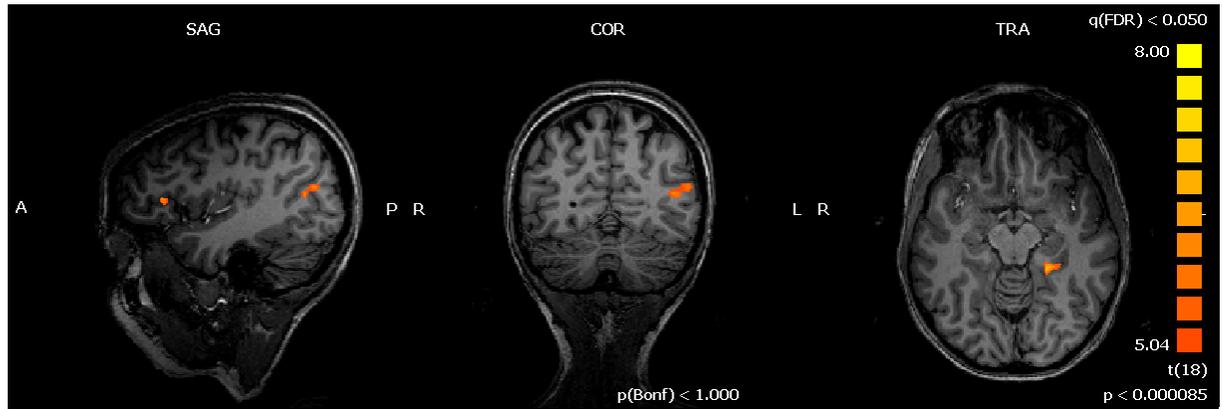

b. Abstract-AnR *vs* VS

Statistical parametric maps of the t-contrast between (a) Picture AnR *vs* VS and (b) Abstract-AnR *vs* VS showing areas responding to analogical reasoning thresholded at q(FDR) <0.01.
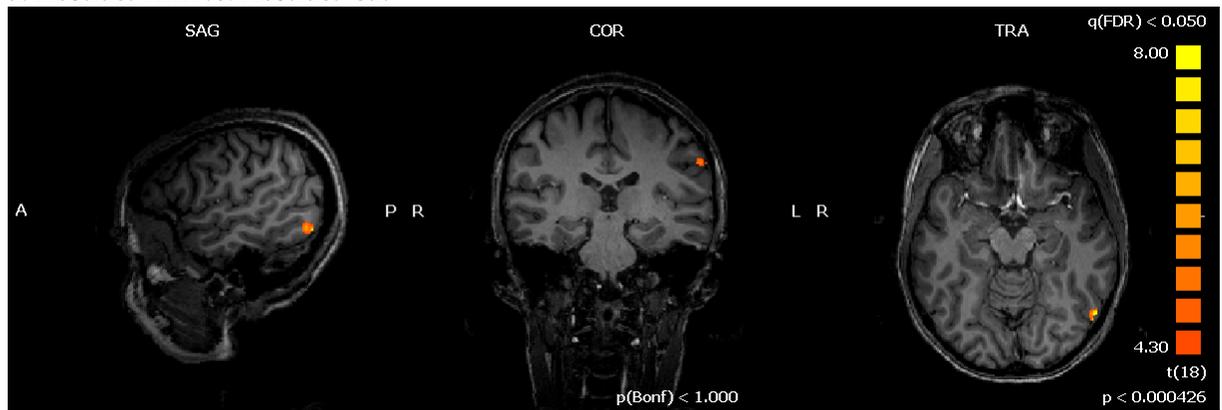
The analogical reasoning in the picture context respect the semantic categorization is associated with a greater involvement of the left inferior frontal gyrus (BA45),the posterior part of left superior/middle temporal gyrus and left parahippocampal gyrus (Table 4.2 and Figure 4.6.a). In the abstract context analogical reasoning respect to categorization evoked greater activity in left superior parietal lobe (BA40) and left occipital cortex (Table 4.2 and Figure 4.6.b).

Fig.4.6 Analogical reasoning *vs.* categorization tasks

a. Picture-AnR *vs.* Picture-Cat
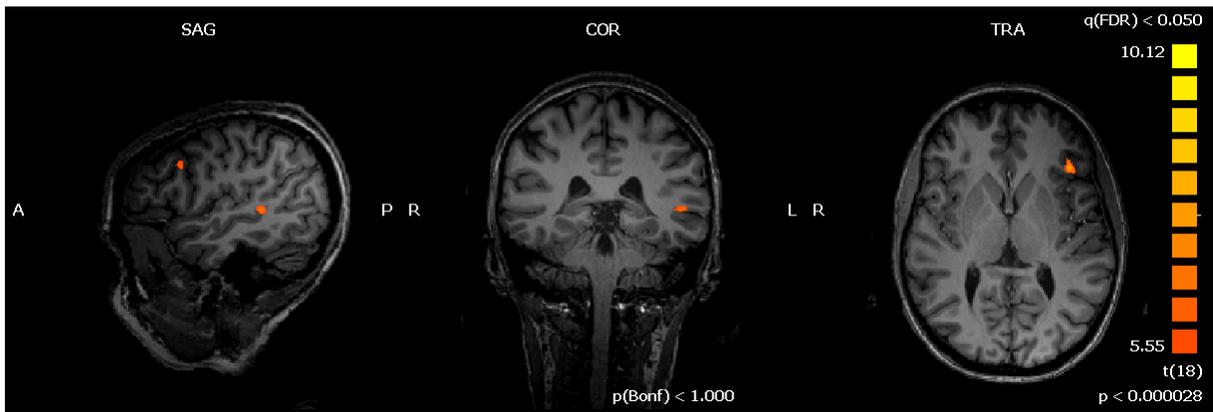

a. Abstract-AnR *vs.* Abstract-Cat

Statistical parametric maps of the t-contrast between (a) Picture AnR *vs* Picture Cat and (b) Abstract-AnR *vs* Abstract-Cat showing areas responding to analogical reasoning thresholded at q(FDR) <0.05.

The picture AnR respect to Abstract AnR is associated three foci of greater activation within the left hemisphere in the BA9, BA45 and in the posterior portion of middle temporal gyrus (Figure 4.7.a). Abstract analogical reasoning respect to picture analogical reasoning was associated with a greater activation in right parietal lobe (Figure 4.7.b).

Fig.4.7 Areas responding to analogical reasoning in the different contexts

a. Picture-AnR *vs.* Abstract-AnR

b. Abstract-AnR *vs.* Picture-AnR
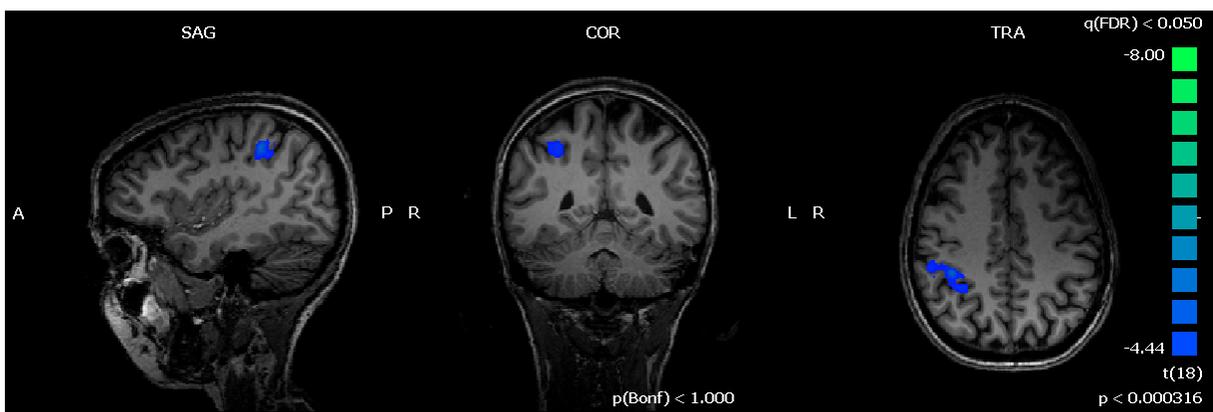
Statistical parametric maps of the t-contrast between (a) Picture (AnR-Cat) *vs* Abstract (AnR-Cat) and (b) Abstract (AnR-Cat) *vs* Picture (AnR-Cat) showing areas responding to analogical reasoning thresholded at q(FDR) <0.05.

Significant interaction between Task X Context was found in the left IFG (BA45), posterior part of left middle temporal gyrus (pMTG BA22) and in the left middle frontal gyrus (BA9).

Since activations observed in BA 9, BA 45 and BA 22 in this study overlapped with those found active in analogical tasks of our previous study, a ROI analysis and a post-hoc t-test was conducted on them. The specific ROI definition was based both on functional and anatomical criteria. The three clusters of activity were intersected with the activations of the previous study and then with anatomical masks using the Talairach Client software (Lancaster, et al., 2000) in order to exclude voxels belonging to adjacent regions from the analysis.

Both BA45 and pMTG displayed a significative higher response in pictures analogical reasoning respect to the semantic categorization (Picture-AnR *vs*. Picture-Cat: BA45 p=0.001; BA22 p=0.001) and respect to abstract reasoning (Picture-AnR *vs* Abstract-AnR: BA45 p=0.007; BA22 p=0.001). Both areas showed a negative response in abstract reasoning and low positive response in abstract categorization.

Differently from BA45 and BA22, BA9 showed a positive response in all tasks and it was involved to a similar extent in abstract and picture contexts (Pictures *vs* Abstract: p=0.4) and in the AnR and Cat tasks (Pictures *vs* Abstract: p=0.7; Picture-AnR *vs* Abstract-AnR p=0.7; Picture-Cat *vs* Abstract -Cat p=0.08). The only significant difference within the BA9 was found within the abstract context (Cat *vs* AnR p=0.003).

Figure 4.8 ROI Analysis
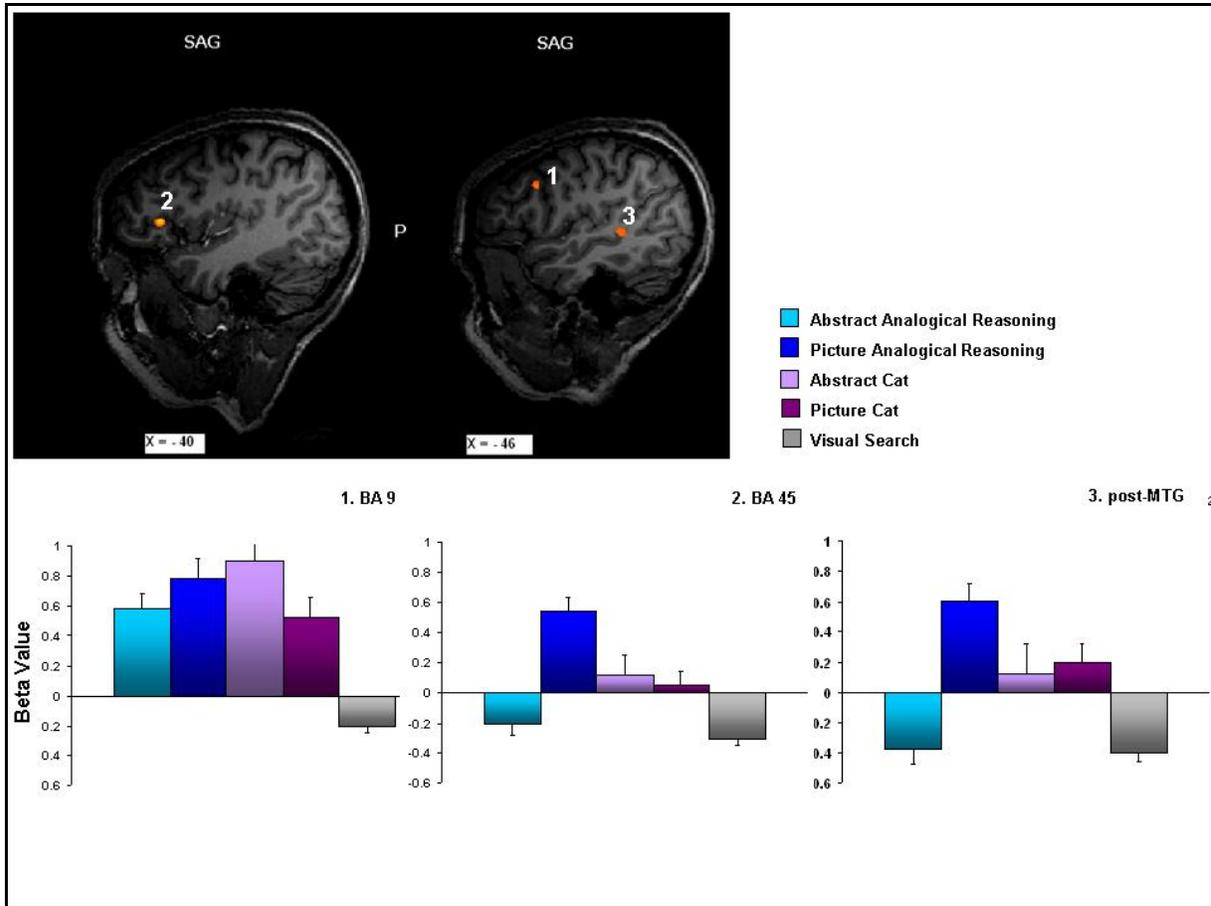
ROI analysis of the left areas described in the results section. The plots depict the mean normalized beta values for the five conditions. Abbreviations: BA = Brodmann Area.

Table 4.1 Context effect

Area	Talairach Coordinates			Nr of Voxels	BA
	x	y	z		
Picture *vs* Abstract					
R Middle Frontal Gyrus	40	35	24	834	46
R Fusiform Gyrus	27	-40	-14	8053	37
L Fusiform Gyrus	-32	-27	-13	12370	37
L Inferior Frontal Gyrus	-43	26	0.15	5205	45/46/47
L Middle Temporal Gyrus	-47	-36	-1.9	994	22
Abstract *vs* Picture					
Bilateral Sup & Inf Parietal Lobule	11	-56	41	21920	40/7
R Precentral & Inferior Frontal Gyrus	49	2.1	32	1358	6
Picture (AnR-Categ) *vs* Abstract (AnR-Categ)					
L Middle Temporal Gyrus	-49	-39	0.27	288	22
L Inferior Frontal Gyrus	-39	27	5.1	178	45
L Inferior Frontal Gyrus	-39	27	5.1	60	9
Abstract (AnR-Categ) *vs* Picture (AnR-Categ)					
R Supramarginal Gyrus	37	-41	39	1879	40

Table 4.2 Task effect

Area	Talairach Coordinates			Nr of Voxels	BA
	x	y	z		
Picture AnR *vs* VS					
R Inferior Frontal Gyrus	43	17	24	771	46
R Inferior Frontal Gyrus	30	30	-3.1	522	47
R Middle Occipital Gyrus	40	-69	12	2347	19
R Fusiform Gyrus	29	-47	-13	11091	37
R Insula	33	18	0.65	734	
R Cerebellum	10	-74	-27	483	
Medial Frontal Gyrus	-4.5	15	48	3258	
L Thalamus	-7.8	-13	7.2	466	
L Superior Occipital Gyrus	-31	-71	30	923	19
L Limbic Lobe - Uncus	-32	-6.5	-26	585	28
L Parahippocampal Gyrus	-18	-33	-0.4	723	
L Fusiform Gyrus	-37	-52	-8.2	20124	22/39/37
L Inferior & Middle Frontal Gyrus	-42	20	16	19506	45/46/47/9
Abstract AnR *vs* VS					
Bilateral Parietal Lobe	-12	-51	41	15060	40
R Fusiform gyrus	37	-62	-11	18635	37
R Inferior Frontal Gyrus	44	12	29	5611	9
R Inferior Frontal Gyrus	42	36	2.3	553	46
R Insula	33	17	2.7	2005	
R Frontal lobe	24	-0.82	51	1032	6
Medial Frontal gyrus	0.089	14	44	4326	
R Thalamus	8.3	-13	3.3	507	
L Fusiform Gyrus	-32	-65	-13	23629	37
L Thalamus	-11	-12	7	200	
L Frontal lobe	-24	-0.89	52	1896	6
L Insula	-30	18	4.9	772	13
L Inferior Frontal Gyrus	-41	4	30	4563	9
L Middle Frontal Gyrus	-39	28	25	2002	46
L Middle Frontal Gyrus	-38	41	7.9	396	10
L cerebellum	-11	-52	-41	615	
Picture (AnR *vs* Cat)					
R Sup Temporal Gyrus	48	-52	6.4	37	39
R Middle Temp Gyrus	45	-67	4.1	80	37
L Medial Frontal Gyrus	-8.5	43	34	44	6
L Sup-Middle Temporal Gyrus	-41	-67	14	923	39/22
L Inferior Frontal Gyrus	-39	26	5.3	88	45
Abstract (AnR *vs* Cat)					
L Middle Occipital Gyrus	-51	-65	-11	142	37
L Inferior Parietal Lobe	-59	-25	31	128	40

Discussion

The present study, where the analogical reasoning had to be performed either within picture or abstract visuo-spatial contexts, was developed in order to confirm and implement the results of the previous studies on pictures and words.

First of all, results of this study confirm that the posterior portion of the middle/superior temporal gyrus and the anterior part of the inferior frontal gyrus (BA45) play a critical role in analogical reasoning on meaningful stimuli. In fact, these areas display a strong and selective activation in picture analogical reasoning respect both to semantic categorization and reasoning on abstract items. Moreover, as suggested in the introduction and coherently with the results available in the literature, the dorsolateral prefrontal cortex (BA9) confirms its context-independent activity and its sovramodal involvement in tasks which require active manipulation and monitoring of information within working memory (Petrides, 2000; Ramnani & Owen, 2004).

Regarding the role of core language areas (BA 44 and BA 22) in reasoning, the present results partially diverge from the previous ones. The absence of activation within the Broca's area during analogical reasoning on pictures confirms that the language component related to the phonological processing is not mandatory for reasoning. One may expect that reasoning on abstract material, which does not convey any a priori information about possible relations, may rely more on covert

verbalization strategies to facilitate the reasoning. Nevertheless, since reasoning on abstract material did not engage brain structures related to the verbalization, our data lead to a possible different scenario where verbalization may be not critical for reasoning. The main evidences of the literature about the role of inner verbalization in cognition and problem solving comes from studies on healthy participant using verbal shadowing (Hermer-Vazquez, et al., 1999) or articulatory suppression (Baldo, et al., 2005) and from studies on aphasic patients (see Baldo et al. 2005). However, verbal shadowing and articulatory suppression also cause an interference effect because the attentional and cognitive resources have to be divided between multiple tasks/informations and this, in turn, may be enough to interfere with reasoning. Regarding the patients studies it must be taken into account that most of them were performed on stroke patients with large lesions that usually involve other areas beyond those critical for language. Thus, the association between aphasia and reasoning impairment may be due just to spatial proximity of brain areas that may be otherwise distinct in their functions such as BA44 and BA45/47 that, despite being all comprised in what is defined as Broca's area, probably subserve very different operations related respectively to phonology and relational integration (Barwood et al., 2011; Dronkers, Wilkins, Van Valin, Redfern, & Jaeger, 2004; Thompson-Schill, 2005).

The divergence within the language core areas between this study and the first one presented in this work concerns the modulation of the posterior part of the middle/superior temporal gyrus. In fact, in the current study this region showed a strong activation when analogical reasoning had to be performed within a picture context, while it displayed a low level of activity in the same task and context in the

previous study on adults. Thus, despite the possible role of posterior superior/middle temporal gyrus in lexical-phonological access (Graves, et al., 2008), altogether our data suggest that the processing performed by this area may specifically contribute to reasoning. This region and the adjacent areas within the superior temporal sulcus has been defined the "chameleon of human brain" (Hein & Knight, 2008). In the last years it has been linked to various and different functions in different domains such as social perception (Saxe, 2006), face processing (Haxby, Hoffman, & Gobbini, 2000), lexical-semantic integration (Friederici, et al., 2009), speech perception (Price, 2000) and cross-modal binding (Beauchamp & Martin, 2007; Hocking & Price, 2008). Despite the more anterior activations within this area are usually more related to language and the posterior ones to non-language processing, in a recent meta-analysis it has been proposed that the functional load of posterior superior temporal sulcus and adjacent regions is determined more by the functional characteristic of coactiveted higher order areas rather than by a functional fragmentation itself (Hein & Knight, 2008). In other words, it may subserve different cognitive functions in relation to a network of coactivations. In this scenario it is possible to argue that the posterior middle temporal gyrus may play a role in integration of information relevant for the reasoning interconnected with the frontal cortex, and specifically with the anterior part of inferior frontal gyrus (BA 45), which appears to be critical for analogical reasoning.

The BA45 showed a selective response for picture analogical reasoning being almost silent during the semantic categorization task. This finding support the idea that its activity is not linked to the semantic retrieval per se but is required for some additional cognitive operation needed for analogical reasoning. In fact, compared to

semantic categorization, solving an analogy requires the reasoner to perform a further cognitive step to comprehend if the relations between the two pairs of items are the same. Gentner (2000) distinguishes between low-order relations and high order relations. The first, also called "conventionalized semantic relations", represent the relation among items. The high-order relations, also called "abstract relation", represent the relation among low-order relations and are built upon the comparison of conventionalized semantic relations to verify if they are the same. This process is the key to analogical thought and it is known as analogical mapping (Gentner, 2003). The analogical mapping requires more than simply identifying conventionalized semantic relations within each item: it involves an alignment process whereby the elements of one pair are aligned one-to-one with corresponding elements of the other pair (A:C and B:D). In other word, the analogical mapping involves the comparison of the conventionalized semantic relations between the pairs, but also a "vertical" process of comparison of the single items. Thus, it may be argued that the BA45 plays a specific role in this process of alignment and integration between items and pairs. However, BA45 appears to be active during analogical reasoning only when meaningful items are presented while it appeared to be silent during reasoning within an abstract context. This lack of activation of inferior frontal gyrus in abstract reasoning is in contrast with current data available in the literature where reasoning is performed on semantic-free material such as analogy on geometric stimuli (Wharton, et al., 2000), Raven's Progressive Matrices-like tasks (Christoff, et al., 2001; Prabhakaran, et al., 1997), letter-string analogy (Geake & Hansen, 2005) and visuo-spatial reasoning (Krawczyk, et al., 2011; Wartenburger, et al., 2009). In what follows we try to explain

the discrepancy between these findings and our results. Our abstract reasoning task was based on visuo-spatial reasoning where the conventional semantic relations among items were arbitrary defined as spatial transformation (rotation and translation). Thus, as expected according to the literature (Lamm, Windischberger, Moser, & Bauer, 2007; Wartenburger, et al., 2009; Zacks, 2008), compared the visual search task, we observed high activation within a bilateral fronto-parietal and occipital network known to be involved in visuo-spatial working memory tasks and mental rotation tasks. Part of the activation in occipital cortex and superior parietal lobe may be due also to higher attentional demands in relation to the abstract reasoning condition, as confirmed by subjective reports of the participants and longer response time recorded for this task compared to all other tasks. Despite all these activations were expected, we developed the task assuming that the extraction and comparison of the type of spatial transformation in the two pairs of items engaged the cognitive processes at the base of analogical reasoning, similar to those active for the picture analogy task. In our planning, the main factor we wanted to investigate comparing reasoning on pictures to abstract items was the role of semantic information that, by definition, is embedded in the first ones and absent in the second ones. It would follow that the role of the activity of BA45 may be required only when the analogy is performed manipulating semantic knowledge. More in general, it could be suggested that the activity of the inferior frontal gyrus may be related to reasoning within domains where conventionalized semantic relations are already known to the subject. This interpretation may partially reconcile our results with the literature with reasoning studies with supposedly semantic-free material that found an activation of

BA45, if we consider that, at least on some of those studies, participants had to reason on items or patterns that where not completely empty of meaning such as letter strings (Geake & Hansen, 2005) or nameable geometrical pictures (Wharton, et al., 2000). In our task the participants could not rely on any acquired knowledge conveyed by the items because they represented true novel abstract meaningless pictures, thus none stimuli-related knowledge could be manipulated. A second possible interpretation of the lack of activation within BA45 during reasoning with abstract items may relate to substantial differences in the reasoning algorithms implied by our two tasks. It is possible that the model of analogical mapping proposed by Gentner did not fully apply to our abstract task since in this condition the one-to-one alignment between corresponding elements of the pairs is not informative respect to the problem solving. Thus, the subject had not to pass through this step to solve the task and had to verify only if the same arbitrary defined rules were applied to both pairs of items. In this respect, despite being apparently similar to an analogy problem, our abstract reasoning may be possibly reduced only to visuo-spatial reasoning. In order to further explore this hypothesis it would be needed to develop an analogy task on abstract items where all steps of analogical reasoning are involved, including the vertical alignment across pair of items.

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General conclusions

This work investigated the relationship between reasoning and language looking at how the different contexts of reasoning modulate/influence the brain activity. A second aspect that was partially tackled relates relational reasoning in developmental dyslexia and how this language impairment may influence the brain organization for higher cognitive function traditionally linked to verbal language.

Concerning the first point, overall our data suggest that, since it exists a sovra-modal system subserving reasoning within the dorsolateral prefrontal cortex, the different features of the terms of analogical reasoning differently engaged and modulated brain activity in relation to their verbal and semantic content.

The pictures reasoning appears to be specifically related to the activity of the anterior part of inferior frontal gyrus (BA45) and to brain areas known to subserve the semantic system, while abstract reasoning involved a fronto-parietal-occipital network linked to the visuo-spatial domain and to the higher attentional engagement related to the complexity of abstract reasoning condition. Notably, only reasoning on words triggered the lexical-phonological system while, when the lexical-phonological analysis

was not explicitly required (pictures) or not possible (abstract stimuli), the reasoning could be performed without the language involvement, at least in its phonological/sub-articulatory component. In a condition of phonological impairment such as the dyslexia, the use of core language areas involved in this process is avoided when the task (pictures analogical reasoning) does not require a mandatory lexical-phonological access. Visual information conveyed by a picture is enough to perform an analogy among items without passing through any verbal label. Thus, the role of verbal language seems to be limited to decoding arguments of reasoning, rather than to the reasoning itself, for example trough a covert verbalization, at least in healthy adults. The results on young normal readers, who activated core language areas also in picture reasoning, suggests the possibility that in early age the resolution of analogy may be facilitated by verbal strategies.

The constant involvement of the anterior part of the left inferior frontal gyrus during analogical reasoning strongly suggests that it plays a key role in this kind of reasoning, possibly in relation to extraction, mapping and comparison of the relationships between terms. The lack of activation in this area during abstract reasoning, however, posits some problem to this interpretation suggesting that the activity of BA 45 may be evoked only when the terms of the analogy belong to the semantic domain. This hypothesis may be object of furthers investigations using meaningful and meaningless stimuli within different type of tasks (e.g. multiple choices analogical reasoning) beyond the classical "A:B as C:D".

The involvement of the posterior part of the left middle/superior temporal gyrus for analogical reasoning is less clear, despite the data suggested its specific role in

analogical reasoning within the semantic domain. The divergence of our results and the state of art in the literature about the functional role of this region does not allow to formulate a specific hypothesis: it may support a lexical–semantic integration or a more general process of concept integration showing a developmental trajectory in relation to the maturation of anterior regions.

Regarding the contribution of the present work to our understanding of developmental dyslexia, the neuropsychological data collected support the idea that dyslexia is characterized not only by specific weaknesses (e.g. phonology, working memory) but also by cognitive strengths that may be represented by problem solving, especially within the non-verbal domain. Further investigations are required to explore the possible dissociation in developmental dyslexia between the executive functions - such as working memory, rapid automatic shifting, automatization - and others executives functions - i.e. planning and problem solving - and their relationship with the different aspects of reading abilities (grapheme-phoneme conversion, text comprehension).

The fMRI investigation allows to exclude that reading impairment may induce a deep brain reorganization and/or the recruitment of a compensatory system during reasoning. Despite that, the presence of the reading disorder induces a different modulation in relation to the context on brain areas devoted to reasoning and sustains the hypothesis of different strategies used to solve the analogy on picture. In fact, the data suggest that the reading disorders did not affect the efficiency of reasoning on pictorial material and the brain areas activated revealed that dyslexics and normal

readers rely on different strategies to reason. In particular, when the task did not require a mandatory lexical-phonological access, dyslexics avoided the use of core language areas involved in this process while young normal readers relied on verbal language within all contexts. A possible interpretation of these results is that young dyslexics implement a more efficient way of solving an analogy task displaying a pattern that is more similar to adults and their more localized brain activations during analogical reasoning may reflect a more efficient neural circuit. If this is the case, it would be worthwhile investigating the role of BA 45 and of the posterior portion of middle temporal gyrus as parts of a compensatory system for reaching reading efficiency in adult dyslexics.

If future studies will confirmed the idea that dyslexics implement a more efficient way to reason, it would be interesting to go more in depth exploring differences in the patterns of brain activity during reasoning across different domains and across ages. Knowing how the brain implement alternative ways to solve the same task may have implications in the rehabilitation and teaching to guide language impaired subjects in developing efficient strategies for reasoning and learning.

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Chapter VI

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