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Patterns of brain reorganization subsequent to left fusiform damage: fMRI evidence from visual processing of words and pseudowords, faces and objects

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Abstract

Little is known about the neural reorganization that takes place subsequent to lesions that affect orthographic processing (reading and/or spelling). We report on an fMRI investigation of an individual with a left mid-fusiform resection that affected both reading and spelling (Tsapkini & Rapp, 2010). To investigate possible patterns of functional reorganization, we compared the behavioral and neural activation patterns of this individual with those of a group of control participants for the tasks of silent reading of words and pseudowords and the passive viewing of faces and objects, all tasks that typically recruit the inferior temporal lobes. This comparison was carried out with methods that included a novel application of Mahalanobis distance statistics, and revealed: (1) normal behavioral and neural responses for face and object processing, (2) evidence of neural reorganization bilaterally in the posterior fusiform that supported normal performance in pseudoword reading and which contributed to word reading (3) evidence of abnormal recruitment of the bilateral anterior temporal lobes indicating compensatory (albeit insufficient) recruitment of mechanisms for circumventing the word reading deficit.

Keywords

functional reorganization; reading; fusiform gyrus; Mahalanobis; anterior temporal lobe

1. Introduction

Research directed at understanding the neural reorganization that takes place subsequent to acquired language impairments is still in its very early stages. Functional neuroimaging methods have recently provided important opportunities to reveal the neural mechanisms that support the recovery of language functions. The aim of this paper is to use fMRI to examine patterns of neural response in the case of an individual with damage to the left

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fusiform gyrus that produced impairments in written language processing. We examine the relationship between behavioral and neural responses for tasks involving functions that normally make use of the left fusiform or nearby areas – word and pseudoword reading as well as object and face processing.

Research to date has examined neural reorganization both in spontaneous recovery of language functions (Cao et al., 1999; Perani et al., 2003) as well as subsequent to therapeutic interventions (Belin et al., 1996; Thompson et al., 2009). This work has provided evidence that various mechanisms may be involved in language recovery, including: recruitment of contralesional substrates homologous to the lesion, recruitment of perilesional substrates, and recruitment of other ipsilesional substrates non-adjacent to the lesion (for a review see Thompson & den Ouden (2008) and also discussions in Crosson et al., 2007; Fridriksson et al., 2007; Heiss et al., 1999; Price & Crinion, 2005; Saur et al., 2006; Selnes et al., 1999; Thompson et al., in press; Vitali et al., 2007; Warburton et al., 1999). The most widely proposed mechanism is recruitment of right hemisphere substrates, typically substrates homologous to the left hemisphere lesion (Basso et al., 1989; Liepert & Weiller, 1999; Meinzer et al., 2007; Peck et al., 2004; Perani et al., 2003; Raboyeau et al., 2008). However, this proposal has been challenged by findings indicating that the right hemisphere recruitment may be only the early response of the brain but may not be support the ultimate recovery of function (Fernandez et al., 2004; Heiss et al., 1999; Ino et al., 2008; Saur et al., 2006; Warburton, et al., 1999). Some of this work indicates that recovery of function after at least 6 months post-injury was associated only with the recruitment of left hemisphere areas either adjacent or non-adjacent to the lesioned areas. Several papers have described some of the many methodological and interpretative challenges faced by these investigations (e.g., Price and Friston, 1999; Bonakdarpour et al, 2007), making it clear that strong conclusions remain difficult for the time being given the complexity of the research in this area.

1.1 Functional neuroimaging in cases of acquired written language impairments

Generally speaking, two approaches are taken in functional neuroimaging studies directed at understanding neural changes supporting recovery of language function. One approach is to carry out an intervention (treatment study) with neuroimaging taking place pre and post intervention; another approach is to compare neural activations from an individual suffering from an acquired language impairment with the activations of neurologically intact individuals. The logic is that neural areas that show differences from pre to post intervention and/or differences between the experimental subject and controls are candidates for neural substrates supporting recovery. While both types of studies have been more common in the area of spoken language than written language, the literature on written language deficits is steadily growing. However, these studies have exclusively been concerned with reading, rather than spelling deficits.

In terms of intervention studies, several have examined neural reorganization in individuals with acquired phonological alexia (difficulty reading nonwords, often accompanied by difficulty in function word reading). Small et al. (1998) examined neural activation changes before and after training to improve sublexical grapheme-phoneme processing in an individual with a left fronto-temporal lesion. Behaviorally, they found that the training improved reading accuracy for nonwords and function words and that this improvement reflected the improved operation of sublexical processes. Neurally, they found that the primary changes involved a shift in activation from the left angular gyrus to the left lingual gyrus. Adair, et al (2000) used SPECT to study cerebral blood flow(CBF) in an individual with a lesion affecting left hemisphere posterior superior and middle temporal gyri as well as adjacent temporal-parietal and temporal-occipital cortex. They examined changes in the CBF during nonword reading before and after treatment targeted at phonological analysis and letter-sound mappings. They found post-treatment recruitment of right hemisphere

perisylvian areas as well as left hemisphere frontal areas. In a more recent study, Kurland and colleagues (2008) considered an individual with a left temporal-parietal lesion and they examined the effects of a semantic treatment designed to improve the reading of function words and abstract words. They found that for words that had been "overlearned" to near normal levels of reading accuracy, activation shifted pre- to post-treatment from the right hemisphere to perilesional areas of the left parietal lobe as well as to the left anterior temporal lobe. Interestingly, all three studies reported ipsilesional neural changes that were not restricted to the perilesional region and that were assumed to be related to the specific treatment approaches that were applied.

With regard to functional neuroimaging studies comparing individuals with deficits to normal controls, the majority of these have involved an acquired reading impairment known as "letter-by-letter reading" or "pure alexia". This impairment is identified behaviorally by the strong effect of length on reading times, hence the term "letter-by-letter" reading. The lesions typically affect posterior left hemisphere temporal and occipital areas, often (although not always) accompanied by some involvement of the posterior callosal pathways (Damasio & Damasio, 1983; Binder & Mohr, 1992; Cohen et al., 2002). The primary interest has been in characterizing the differences in activation patterns between normal readers and letter-by-letter readers in order to understand the normal functions of the lesioned substrates as well as to identify the neural substrates that support this abnormal reading "strategy". In terms of identifying substrates recruited in normal reading, this work provides strong support for the role of inferior temporal areas in reading, highlighting the importance of the region of the mid-fusiform/occipito-temporal sulcus (sometimes referred to as the Visual Word Form Area or VWFA) (Cohen et al, 2000, 2002). In terms of neural changes that apparently support the letter-by-letter reading behavior, the neuroimaging data from these cases converges on identifying increased involvement of the right hemisphere homologue of the VWFA, right hemisphere occipital areas and left hemisphere fronto-parietal regions. This recruitment pattern forms the basis of the proposal that, in these cases, letters may be recognized in the right hemisphere occipital and VWFA areas, tranfered serially to the left hemisphere and then processed through the left hemisphere fronto-parietal verbal working memory network. This results in eventual word recognition, with possible top-down recruitment of the left VWFA (Cohen et al., 2003, 2004; Henry et al., 2005, and Gaillard et al 2006; see also Pyun et al., 2010 for convergent evidence involving Korean).

1.2 The role of the inferior temporal region in written language processing

In functional neuroimaging studies of neurologically intact individuals, the area of the left hemisphere mid-fusiform gyrus/occipito-temproal sulcus has been identified as an important component of the reading network (Baker et al., 2007; Binder et al., 2003, 2006; Booth et al., 2002; Carreiras et al., 2007; Cohen et al., 2000, 2002, 2004; Dehaene et al., 2002, 2004; Fiez et al., 1999; Indefrey et al., 1997; Kronbichler et al., 2007; McCandliss et al., 2001; Mechelli et al., 2005; Moore & Price, 1999; Pugh et al., 1996, 2001; Rapp & Lipka, in press). The neuroimaging findings are consistent with lesion/deficit correlation studies of individuals with acquired reading impairments (Behrman et al., 1992, 1998; Damasio & Damasio, 1983; Hillis et al., 2001; Gaillard et al., 2006; Leff et al., 2001; Marsh & Hillis, 2005; Philipose et al., 2007). Furthermore, in addition to its role in reading, this region has also been implicated in spelling both in lesion/deficit correlation studies (Rapcsak and Beeson, 2004 Rapcsak et al. 2007, 2009; Rapp, 2002; Tsapkini & Rapp, 2010) as well as in functional neuroimaging studies with neurologically intact participants (Beeson, et al., 2003; Purcell, et al, 2009; Rapp & Lipka, in press). Nonetheless, it is important to note that the specific role of this region is still under investigation with vigorous debate regarding whether its role is specifically orthographic (see Price & Devlin, 2003; 2005; Starrfelt & Gerlach, 2007; Hillis et al., 2005). In this regard, particularly strong evidence of the

orthographic role of this area in written language processing comes from two recent case studies, both involving resections of the left hemisphere fusiform gyrus.

Gaillard et al., (2006) described an individual who underwent a left posterior fusiform resection. Functional MRI scanning both before and after resection allowed measurement of neural changes to be related to pre to post-lesion behavioral changes. Pre-surgery, fMRI and behavioral testing revealed normal neural responses to faces, objects and written stimuli. Post-surgery, behavioral testing revealed specific deficits affecting reading but not the processing of other visual stimuli such as faces, objects and tools. In addition, post-surgery fMRI revealed that the normal pre-surgery fusiform responsiveness was disrupted, but only for written word processing. The authors concluded that the evidence provided strong support for the claim that the left fusiform gyrus is necessary for the visual processing of words but not for other visual categories (e.g., Bar et al., 2001; Dehaene et al., 2005; Devlin et al., 2006; Gauthier et al., 2000; Joseph et al., 2003; Yovel & Kanwisher, 2002;.

Tsapkini & Rapp (2010) described an individual who also underwent a resection of the left fusiform gyrus, anterior to the resection in the case reported by Gaillard et al. (2006). As a result, this individual suffered a specific disruption affecting both the reading and spelling of words, but sparing orthographic processing of pseudowords, auditory processing of words and visual processing of visual objects and faces. The reading deficit was not of the letter-by-letter type reported in many of the studies by Cohen and colleagues, but instead specifically involved accessing semantics from the written form (and vice versa in spelling). For present purposes, the key finding is that the persistence of reading and spelling deficits several years after the fusiform resection strongly supports the hypothesis of a key role for this region in orthographic processing.

1.3 Understanding functional reorganization: Patterns of neural and behavioral responses

In this paper we report on an fMRI investigation of the individual described in Tsapkini & Rapp (2010) (initials DPT) that allowed us to evaluate questions of functional reorganization. For this case, it would be important to understand how the impaired reading and spelling functions were accomplished in the face of the resection of a key component of the reading and spelling networks, and also whether the spared abilities were supported by intact substrates or whether, as a result of functional reorganization, these intact processes relied on substrates not normally used for these functions. To address these issues, we examined DPT's neural responses to reading, object and face processing and compared them to those of neurologically intact participants. Our goal was to identify clear similarities and differences in neural activation patterns for the damaged and undamaged brains and, in turn, relate these to DPT's pattern of spared and impaired cognitive functions.

Written words, pseudowords and visually presented faces and objects are all stimuli which, in neurologically intact individuals, reliably recruit neural substrates in the inferior temporal/fusiform region. With regard to visual object and face processing, it is generally assumed that the left fusiform gyrus is often active but not necessary for object and face processing (e.g., DeLeon et al, 2007; Downing et al., 2006; Grill-Spector & Kanwisher, 2005; Joseph et al., 2003), with the necessary substrates corresponding to right-hemisphere fusisform and adjacent areas (Hasson, et al., 2002; Hemond et al., 2007; Grill-Spector et al., 2004; Kanwisher and Yovel, 2006; Kleinschmidt and Cohen, 2006; Yovel and Kanwisher, 2007). Written word and pseudoword processing, present a complementary picture in which, as already indicated, the left mid fusiform gyrus is, arguably, critical for orthographic processing while right mid fusiform activations are often observed, but not believed to be necessary.

The logic of studies comparing activation patterns of impaired and control individuals involves the examination of the relationship between the patterns of spared and impaired cognitive functions on the one hand and the patterns of normal and abnormal neural responses, on the other. In this way, these types of studies can shed light on functional reorganization. There are three types of relationship patterns that one might observe for the set of cognitive functions evaluated. *Type1: Normal behavior/Normal neural response*. Both the behavioral data and the neural data are comparable to those produced by neurologically intact individuals. This would indicate that the lesion did not affect substrates necessary for a particular cognitive function. *Type 2: Normal behavior/Abnormal neural response*. The behavioral data indicate that cognitive processing is intact despite the recruitment of neural substrates that differ from those of neurologically intact individuals. This pattern indicates that although the lesion has affected the neural circuit for the particular cognitive function, successful functional reorganization has occurred. Furthermore, this pattern allows for the inference that the specific substrates that are active in the case of neural injury but not in the neurologically intact individuals play an important role in the successful recovery of function. *Type 3: Abnormal behavior/Abnormal neural response*: The abnormal behavioral response indicates both that the lesion has affected the relevant neural circuitry and that full functional reorganization has not occurred. The abnormal neural response may consist of failure to recruit areas normally recruited and/or the recruitment of areas not normally recruited. The recruitment of areas not observed in the neutrally intact individuals may have multiple interpretations, for example: (a) these areas may have successfully replaced a subset, but not all, of the impaired operations; (b) these areas may represent the activation of normally instantiated functions not normally used but that are recruited in an unsuccessful attempt to compensate for the deficit; or (c) these areas may represent recruitment of novel substrates to replace the impaired operations but these are inadequate for replacing the disrupted cognitive operations.

In the study we report on in this paper, we describe all three types behavioral-neural patterns in response to damage, revealing recruitment of both ipsi and contralesional neural substrates in reading. The results provide a basis for understanding the reorganization of written language functions that may occur after damage to the left fusiform gyrus.

2. Case Study

DPT was a right-handed, law school graduate (DOB: 9/1969) who underwent surgical resection of an oligodendroglioma in the left fusiform gyrus (2001). Immediately after the surgery he had difficulties in spoken naming, reading comprehension, spelling and short-term memory. However, he was able to resume his employment as an attorney one month later and to then continue working successfully through the time of this investigation. Nonetheless, he continued to experience mild difficulties in reading, moderate difficulties in spelling and occasional anterograde memory difficulties. He reported that, prior to the surgery, he had read extensively for work and that his spelling was comparable to that of fellow law-school graduates. The structural and functional MRI scanning reported here were carried during the same period as the behavioral testing summarized below and reported in detail in Tsapkini & Rapp (2010).

The resection lesion (see Figure 1) comprised a large portion of the left fusiform gyrus as well as some areas of the inferior temporal gyrus primarily along the anterior and the lateral edges of the lesion. In terms of Talairach coordinates, the lesion extended along the medial-lateral axis from approximately −29 to −63, along the anterior-posterior axis from −15 to −66, and along the superior-inferior axis from −30 to −6. It is worth noting that the lesion was largely anterior to the lesion of the individual reported by Gaillard et al. (2007) which extended anteriorally-posteriorally from y= −60 to −80.

2.1 Behavioral Testing

A clinical neuropsychological evaluation 21 months after the resection (6/2003) showed normal or superior performance in virtually all cognitive areas evaluated (verbal working memory, visual perception and memory, fine motor speed and precision, spoken word naming and fluency, oral reading, single word auditory comprehension, and recognition memory for words and faces (see Tsapkini & Rapp, 2010 for details). Subsequently, during the period of 7/2005-8/2007, DPT's performance was extensively evaluated in: (1) orthographic processing (reading of words and pseudowords, visual lexical decision with semantic priming, written synonym judgments and written spelling of words and pseudowords; (2) auditory word processing (auditory lexical decision with semantic priming and auditory synonym judgments) and (3) visual object processing (for faces: fame and profession judgment tasks; for visual objects: spoken picture naming and object comprehension (Pyramids and Palm Trees; Howard & Patterson, 1992). DPT's performance was compared to that of 11 age and education-matched control participants using the Crawford & Garthwaite (2002) modified t-test. On the basis of this testing (summarized in Table 1), Tsapkini and Rapp (2010) concluded that DPT suffered from an orthographic deficit that was both modality and category specific. The deficit was modality specific in that the orthographic modality was affected in both comprehension (reading) and production (spelling), but the auditory modality was spared with regard to auditory comprehension and spoken production of words. Furthermore, the deficit was category specific in that, within the visual modality, only the category of written words but not faces or visual objects was affected.

With regard to the modality specificity of the deficit, a comparison of written and spoken modalities in both word production and comprehension was carried out. In terms of word production, as indicated in Table 1, DPT's spoken picture naming RTs were within normal range for both high and low frequency picture names. In contrast, written spelling to dictation of words was significantly impaired relative to the control group. As concerns word comprehension, both spoken and written word comprehension were compared in two tasks: synonym judgment and semantic priming (the latter embedded within a lexical decision task). For synonym judgment (see Table 1) in the auditory modality, DPT's accuracy and RTs did not differ from normal controls; whereas in the written modality, both accuracy and RTs were significantly different from normal controls. In the semantic priming tasks, two stimuli were presented in close temporal succession on each trial and subjects were instructed to make a lexical decision to the second stimulus, which was either semantically related or unrelated to the first stimulus. Assessment of semantic access is possible as significant priming will occur only if the prime word activates its meaning with sufficient speed so as to facilitate the processing of the upcoming semantically related target. In the auditory version, DPT showed a significant (169 msec) semantic priming effect that was comparable in magnitude to the effects exhibited by individual normal controls. In contrast, in the written modality, DPT's 12 msec priming effect was not significant, and was significantly smaller than the effects exhibited by normal controls, who individually all showed significant priming effects (Table 1). In sum, the contrast between normal spoken language production and comprehension and abnormal written language processing indicates that the deficits exhibited by DPT were largely, if not entirely, specific to the orthographic modality.

With regard to the specific nature of the orthographic deficit, it was argued that lexical orthographic processes were disrupted and sublexical ones were spared. More precisely, the claim was that in reading there was a disruption in accessing meaning from print and, in spelling, a complementary disruption in accessing orthographic forms from meaning. This conclusion was based on the following. In spelling, DPT exhibited both regularity and frequency effects in accuracy (Table 1) and his errors consisted of phonologically plausible

responses (e.g., “sauce” spelled as SOSS). In contrast, pseudowords were spelled highly accurately Similarly, in reading, DPT exhibited normal accuracy and RTs in pseudoword reading, indicating that letter processing, orthographic analysis, grapheme-to-phoneme conversion and general phonological output were intact. However, RTs were abnormally slow in word reading and lexical decision for low-frequency and irregular words (although accuracy was within normal limits). Moreover, as indicated above, he showed no semantic priming in a visual lexical decision task and also exhibited slowed responses in written synonym judgments. This pattern of spared and impaired performance in reading specifically identified the disruption as targeting the orthographic word form system or in subsequent access to semantics from orthographic word forms.

With regard to the category specificity of the deficit, DPT performed no differently from control participants (in terms of both RTs and accuracy) on fame judgments of faces or on forced-choice categorization of professions for famous faces. Furthermore, DPT’s object naming times were comparable to those of controls and he exhibited normal performance on a timed version of Pyramids and Palm Trees (Howard and Patterson, 1992). These results indicated that the processing of visual objects and faces was intact, including access to semantics from these categories of visual stimuli.

To summarize, the behavioral testing produced three clear findings: (1) normal processing and access to semantics for faces and visually presented objects and auditorily presented words; (2) sparing of sublexical (pseudoword) processing in both reading and spelling; and (3) disruption of lexical (word) processing in both reading and spelling, most likely affecting the translation between orthographic word forms and lexical semantics. An fMRI study was carried out to examine the neural response patterns that corresponded to these three behavioral patterns. In particular, we addressed the following questions: (1) Did DPT’s normal behavioral pattern of face and object visual processing correspond to a normal pattern of neural responses? (2) How was DPT’s normal behavioral pattern in reading pseudowords achieved in the context of fusiform damage? and (3) How was DPT’s abnormal behavioral pattern in reading written words reflected in the neural responses?

3. Methods

3.1 Subjects

3.1.1 Control participants—Nine right-handed individuals (8 men and 1 woman) with no history of neurological impairment participated in the study. They were matched to DPT in age (30-42 years old) and education (B.A. degree and higher). All individuals were right-handed according to the Edinburgh Inventory (Oldfield, 1971). They were all native speakers of English (English was their first language and the language in which they were educated) and they had no spelling deficits according to a screening test administered prior to scanning. They were recruited from the Johns Hopkins community and gave their written informed consent to participate in this study that had been approved by the Johns Hopkins Institutional Review Board. One control participant was later excluded due to excessive motion artifacts in his functional MRI data.

3.2 Experimental tasks: Overview

Our primary aim was to identify similarities and differences in brain activations between DPT and the control group for stimuli and tasks known to induce fairly reliable topographies of activation in the inferior temporal/fusiform gyri. We assumed that an understanding of these similarities and differences should provide information about manner and mechanisms of the brain’s response to neural injury. In Task 1 (Object/ Faces Viewing) we examined the neural response to passive viewing of faces and objects relative to a scrambled images

baseline (see Haxby et al., 2001). In Task 2 (Silent Reading) we examined the neural response to silent reading of words and pseudowords with respect to a checkerboard baseline. This contrast of orthographic stimuli and checkerboards is one that has been used extensively in studies of the fusiform's role in reading (Cohen et al., 2000; 2003, 2004). The experimental tasks, stimuli, procedures, imaging parameters, and analyses for both fMRI experiments were identical for all control participants and DPT.

3.2.1 Imaging Parameters—MRI data collection was carried out with a 1.5T Phillips scanner and blood oxygen level-dependent T2* -weighted MRI signal were measured using a gradient echo, echo-planar imaging sequence with the following specifications. For Task 1: repetition time [TR] = 2000 msec, FA = 90 degrees, TE= 40 msec, FOV = 230×115 mm, matrix = 64×64; functional data were collected in 23 interleaved slices, with 5mm slice thickness. For each run, 169 brain volumes were acquired, and the first 3 volumes were discarded to reach equilibrium. For Task 2, the same imaging parameters were used except that the TR = 1,500 msec. For Task 2, for each run, 212 interleaved brain volumes were acquired and the first 4 volumes were discarded to reach equilibrium. Comparable, full-brain coverage was obtained in both tasks. In addition, structural images were acquired using an MP-RAGE T1-weighted sequence to provide anatomical information for registration and 3D normalization to the Talairach and Tournoux atlas (1988). The parameters for the anatomical scan were as follows: TR= 8.28msec, TE= 3.8 msec, matrix = 256×256, FOV = 256×180, 200 slices with1mm thickness.

3.2.2 Data Analysis—Functional data were analyzed using Brain Voyager QX 1.8.6 (Brain Innovation, Maastricht, The Netherlands) and Matlab (The Math Works). Preprocessing included head-motion correction, inter-slice acquisition time correction, temporal high-pass filtering (cutoff: 3 cycles per time course), functional-anatomical co-registration, and normalization to Talairach space. All individual functional data were spatially smoothed using an 8 mm full-width half-maximum Gaussian kernel.

We carried out two sets of analyses of the control data. The first was a random effects analysis that allowed us to situate the average group response with respect to DPT's lesion, comparable tasks reported in the literature, and DPT's activations. In the second, we characterized the control data by considering the response patterns of the individual control participants. While the comparison of DPT's activation with the average group results obtained in a random effects analysis is useful, we assumed that the critical analyses would be those involving the comparison of DPT's activations to those of individual neurologically intact participants. While not without its problems, this allows for a determination of the extent to which DPT's neural responses patterns were aberrant relative to the range of other individuals. In this analysis we focus on the cluster activation peaks (location and intensity) rather than activation volumes. Although activation volumes are potentially important sources of information regarding normal and abnormal responses, they are highly sensitive to thresholding levels and extremely variable across even neurologically intact participants. Considering activation volumes would have added a layer of complexity to these analyses that would have made interpretation extremely difficult. Given our interest in identifying the location of the activations, we sometimes found it necessary to use different (significant) correction values for different tasks in order to clearly differentiate the activation clusters and their respective peaks. For example, some tasks produced more overall activation than others. As a result, while distinct clusters may have been visible at some relatively less stringent (but significant) p value for the "less active" task, at the same p value for the "more active" task, the activation clusters sometimes merged together and produced large swathes of activation. These were readily decomposed into multiple clusters at more stringent p values that served to "break up" these large clusters and reveal the individual peaks.

With regard to the comparison of DPT with the individual normal controls, the following four-step approach was taken: Step 1: For each subject (including DPT), and for each task, we considered the results of individual whole-brain analysis and identified all significant activation clusters. The neuroanatomical locations of clusters were identified using Talairach Daemon (Lancaster et al., 2000) and these were then confirmed via visual inspection and consulation with Duvernoy's Atlas (Duvernoy, 1999). Step 2: On the basis of the results of Step 1, we established, for each task, what we will refer to as the "normal neural response patterns". These corresponded to the neuroanatomical regions in which at least six of the eight control subjects exhibited significant activation. While we acknowledge that 6/8 is an arbitrary threshold, it does allow us to capture the majority response while allowing for some variability that might be due individual differences in signal/noise. Step 3: We determined whether or not DPT exhibited the "normal activation response patterns" with respect to both peak cluster location and activation intensity. Three outcomes were possible: (a) DPT could fail to show significant activation in an area that was significantly active in at least 6/8 controls; (b) DPT could show significant activation in an area that that was significantly active in fewer than 6/8 of the controls; (c) DPT could exhibit significant activation in an area that was also significantly active in at least 6/8 controls. Finally, Step 4: For those neuroanatomical regions where both DPT and at least 6/8 controls showed activation (outcome c), we evaluated whether the specific locations and peak intensities of DPT's activations were consistent or deviant from the range of locations and intensities observed in the control participants. To evaluate peak cluster intensities, we compared DPT's peak t-values to those of the individual control participants using the Crawford & Garthwaite (2002) modified t-test. To evaluate peak cluster locations, we carried out a Mahalanobis distance (M) analysis that allowed us to quantitatively evaluate whether or not DPT's peak activation locations were outliers relative to those of the controls. For the Silent reading (Task 2) we carried out all 4 of these steps. However, for Face/Object Viewing (Task 1), we were more narrowly focused on whether or not DPT shared with controls the activation topography for faces and objects that is typically found in the inferior temporal area; therefore, for this task, we carried out only Step 4.

3.2.3 Mahalanobis analysis—We used the Mahalanobis distance (Mahalanobis, 1936) metric to evaluate the difference between DPT's peak cluster locations and those of the individuals in the control group. The Mahalanobis distance has been used with MRI data for such diverse tasks as segmenting anatomical brain regions (Kelman et al., 1997), identifying multiple sclerosis lesions (Aït-ali et al., 2005), cluster analysis (Goutte et al., 1999; Smolders et al., 2007) and multi-voxel pattern analysis techniques (Kriegeskorte et al., 2006). The Mahalanobis distance is also a common metric used for outlier detection in biology (Royce et al., 2005) and analytical chemistry (Egan and Morgan, 1998; De Maesschalck et al., 2000). Mahalanobis distance is a better metric than Euclidean distance for detecting outliers in fMRI contrast maps since it is a scale-invariant multivariate measure sensitive to the correlations in the map both within and between the dimensions.

For example, consider the hypothetical situation depicted in Figure 2 in which the activation peaks of two patients are compared to those of a group of control subjects along two dimensions (the method, of course, applies to any number of dimensions). Using a Euclidean distance metric, the distance of each patient from the group mean corresponds to the difference between the x,y values for each patient and the average group x,y values; this difference in distance is represented by a single value. In the hypothetical example depicted in Figure 2, the Euclidean distance from the group mean is the same for the two patients (e.g., 2.34). This is indicated in the figure by the circle representing the 95% confidence interval from the group mean. Any analysis that evaluates the statistical significance of these data, will yield identical results for the two patients, given that the Euclidean distance differences are equal. However, consider that in this example the values of the individual

control subjects are highly correlated in the x and y dimensions. Given the correlation between these dimensions, in evaluating differences of the patient peaks from the group, one would be inclined to give more weight to distances from the mean that differ from this correlation. In the context of our hypothetical example, one would want to give more weight (consider as more "distant") the peak of Patient A than the peak of Patient B . Differences such as these that relate to the nature of the control group's distributions of values along the multiple dimensions will not be captured in the Euclidean distance metric, but are precisely what is considered in the Mahalanobis approach. This can be seen in the ellipsoid that represents the 95% confidence interval generated from the Mahalanobis approach. Also note that Euclidean distance is a subset of Mahalanobis distance such that when the data are distributed such that the distributions among the various dimensions are uncorrelated, both approaches will yield the same results.

In those neuroanatomical regions in which at least 6/8 controls and DPT exhibited significant activation, we identified the voxel with the peak t-statistic in each cluster and extracted its Talairach coordinates. We then computed a Mahalanobis distance for DPT for each cluster with respect to the controls by (i) estimating the center, c, and covariance matrix, S, of the controls' peak locations in the cluster and (ii) computing the squared distance using the standard equation $MD^2=(x-c)^T * S^{-1} * (x-c)$. We assessed the significance of the Mahalanobis distances against the critical value of the chi-square distribution with three degrees of freedom: $X^2(3) = 7.81$ for $p<.05$ (95% percentile). Figures were created by plotting DPT and the control subject's peak voxels and overlying then with a 95% confidence interval ellipsoid centered on c. The ellipsoid was constructed by scaling the covariance matrix by a distance equal to the inverse of the 95% cumulative density function of a chi-square distribution with three degrees of freedom. Eigenvectors and eigenvalues were computed for the scaled covariance matrix. The eigenvectors scaled by the square root of the eigenvalues defined the axes of the ellipsoid. We used Matlab (The MathWorks, 2009) to obtain and plot the Talairach coordinates of each peak and the Thin Junction Tree Filters for SLAM toolbox (Paskin, 2002) to create the ellipsoids.

4. Task 1: Passive viewing of faces and objects

4.1 Stimuli

The stimuli used were photographs of faces and small man-made objects as well as their pixel-scrambled counterparts. The face stimuli consisted of gray-scale photographs of 10 faces (without hair) presented from 4 different visual angles. The object stimuli consisted of photographs of 10 different man-made objects (scissors, chairs, bottles and shoes). Each image represented the object as viewed from one of four different angles (Haxby et al.; 2001), for a total of 40 different images per category (faces or man-made objects). The visual angles subtended by the stimuli were 7.3 (width) and 7.8 (height)degrees.

4.2 Procedures

E-prime 1.2.1 software (Psychological Software Tools, Pittsburgh, PA) was used for stimulus presentation for both Tasks 1 and 2. Stimuli were presented blocked by the categories: faces, objects, scrambled faces and scrambled objects, with each image presented for 500 msec (40 images per block). Subjects were instructed to attentively view each image. There were two scanning runs, each consisting of 16 blocks, 4 from each of the 4 categories, pseudorandomly ordered so that categories were not repeated in consecutive blocks. The stimuli in the two runs were identical but the sequence of blocks was varied across runs. A fixation point was presented before each block for 6 seconds and also at the end of each run for 20 seconds. The total duration of a run was 344 sec.

4.3 Data Analysis

A general linear model (GLM) approach (Friston et al., 1995) was used to estimate parameter values. The data were modeled with regressors for each condition: fixation, faces, man-made objects, 6 additional motion regressors and a regressor representing run number. The time points corresponding to scrambled faces and objects were used as the baseline. The predicted time courses were convolved with the default hemodynamic response function used by BV. Three contrasts were examined: faces vs. baseline, objects vs. baseline and faces vs. objects.

For the random effects group analysis, we applied a cluster-size correction for multiple comparisons (voxel-wise threshold of $p<.0001$, with a corrected $p<.05$). In the individual subject analyses, for the contrasts of faces vs. baseline and objects vs. baseline, a brain-wise Bonferroni correction for multiple comparisons ($p<.05$) was applied. For the more specific contrasts of faces vs. objects a cluster-size correction for multiple comparisons was applied (voxel-wise threshold of $p <.0001$, with a corrected $p<.05$).

4.4 Results and Discussion

4.4.1. Results—As indicated earlier, the focus of the faces/objects task was to determine whether or not DPT shared with controls the topography of activation for faces and objects that is typically found in the inferior temporal area. Because this is the region that forms the almost exclusive focus of interest and consensus in the literature, we report activations in only these areas.

Figure 3 depicts the fusiform activations observed for the group for the contrasts of faces>baseline (depicted in pink) and objects>baseline (depicted in yellow). These are displayed on a structural image of DPT's brain, allowing for an evaluation of the location of these activations relative to DPT's lesion. As can be seen, the group activations are bilateral and, in the left hemisphere, are situated medial to DPT's lesion. Further, control participants exhibited significant activations in the inferior temporal lobe areas that are representative of those reported in the literature for both objects and faces (DeLeon et al, 2007; Downing et al., 2006; Grill-Spector & Kanwisher, 2005; Grill-Spector et al., 2004; Hasson, et al., 2002; Hemond et al., 2007; Joseph et al., 2003; Kanwisher and Yovel, 2006; Kleinschmidt and Cohen, 2006; Yovel and Kanwisher, 2007).

With regard to the individual subject results and comparisons, Tables 2, 3 and 4 report the locations of the fusiform/occipital gyri activation peaks and the peak intensity (t value) of the contrast for individual control participants and DPT for the following contrasts: faces > baseline, objects > baseline and faces > objects.

As concerns the intensity of the contrast at the activation peaks, Crawford and Garthwaite modified t-tests indicate non significant differences between DPT and control participants (t values ranging between 0.6-2.2), except for the right fusiform peak (t=2.8). However, it is worth noting that this effect would not be significant if we correct for the fact that we carried out 6 t-tests in this analysis.

With regard to the locations of activation peaks, it can be seen in Tables 2-4, DPT's activation peaks were all within the control range of Talairach values. This is confirmed by Mahalanobis distance analyses that indicated that the locations of DPT's activation peaks were not different from those of control participants for: (1) the comparison of faces vs. scrambled face baseline, in the left ($MD^2= 4.26$, $p=0.23$) and the right hemispheres ($MD^2= 5.29$, $p= 0.15$); (2) for the comparison of objects vs. scrambled object baseline, in the left ($MD^2= 2.46$, $p=0.48$) and the right hemispheres ($MD^2 = 5.54$; $p=0.14$) and (3) for the comparison of faces versus objects in the left ($MD^2= 4.09$, $p=0.25$) and the right

hemispheres (MD^2= 1.79; p=0.62). The location of the peak activations in the right and left fusiform/occipital regions are depicted for DPT and control participants for the contrasts FACES > scrambled baseline and OBJECTS > scrambled baseline in Figures 4 and 5 (a and b), along with the Mahalanobis-computed 95% confidence interval (shaded oval).

5. Task 2: Silent reading of pseudowords and words

5.1. Stimuli

Stimuli consisted of high and low frequency words, pronounceable pseudowords, consonant strings and checkerboards. There were 80 exemplars of each orthographic category. Words were monomorphemic, ranging in length from 4-7 letters, and were of high or low frequency (Francis & Kucera;1982); both regular and irregular words were included consisting of nouns, verbs and adjectives. Neither regularity nor length were manipulated in such a way that allowed for adequate analysis of the effects of these variables. The design was such that effects of frequency could be evaluated; however, analyses revealed no brain areas showing significant activation differences for high vs. low frequency words either for the control participants or for DPT; therefore this manipulation will not be discussed further. Pseudowords were taken from the MRC Database (Coltheart, 2001) and were matched to the words in length. All orthographic stimuli were presented in lower case letters.

5.2. Procedure

Stimuli were presented in blocks of checkerboards, consonant strings, pseudowords, and high and low frequency words in two scanning runs, with 4 blocks of each stimulus type in each run with 10 stimuli per block, resulting in 200 stimuli in total for each run. Blocks were presented in pseudorandom order, avoiding repetition of the same stimulus type in successive blocks. The order of blocks was varied across runs but was identical for all subjects. Each trial consisted of: 500 msec central fixation cross, followed by a 200 msec presentation of the target and an 800 msec rest period (blank screen). There was also a 6 second fixation period in the beginning of each run and another 12 second fixation period at the end of each run. Each functional run had a duration of 318 seconds and the anatomical scan lasted 383 seconds. Participants were instructed to read silently all the word and pseudoword stimuli. In the case of checkerboards they were instructed to say silently the word ‘checkerboard’. For consonant strings they were instructed to silently say the word “consonants”. However, there was some confusion amongst participants regarding the consonant string instructions; as a result, the consonant string condition was excluded from further analysis.

5.3. Data analysis

The general linear model (GLM) approach (Friston et al., 1995) was used to estimate parameter values. The data were modeled with regressors for each condition: fixation, consonant strings, pseudowords, high and low frequency words, as well as 6 additional motion regressors and a regressor representing run number. The time points corresponding to checkerboards were used as the baseline and were left out of the GLM. The predicted time courses were convolved with the default hemodynamic response used by BV. The following two contrasts were examined: words vs. baseline (checkerboards) and pseudowords vs. baseline (checkerboards) for both the random effects group analyses and the individual subjects analyses. For the random effects group analyses an uncorrected p value <.005 was applied. In the individual subjects analyses, for the pseudowords vs. checkerboards contrast, the correction for multiple comparisons consisted of brain-wise Bonferroni thresholding (p<.05), while for the words vs. checkerboards contrast, cluster size thresholding was applied with an uncorrected voxelwise threshold of p<.0001 and a corrected value of p < .05.

5.4. Results

5.4.1. Results: Silent reading of pseudowords—The random effects group analysis yielded significant activations for pseudowords>checkerboards in the following neuronanatomical regions: left mid-fusiform gyrus, left inferior temporal gyrus, left superior temporal gyrus, bilateral superior parietal lobe/intraparietal sulcus, bilateral inferior and middle frontal gyri. Figure 3 reports the group activations (depicted in green) in the fusiform gyrus, superimposed on DPT's structural MRI. As can be seen, the group activation is limited to the left hemisphere and falls clearly within the area of DPT's lesion.

With regard to the individual subject analyses, Table 5A reports areas in which at least 6/8 normal participants showed significant activations are reported: left intraparietal sulcus (IPS), left inferior frontal gyrus (IFG), left superior temporal gyrus (STG) and left fusiform gyrus (FF). DPT showed significant activation clusters in all of these areas as well and he did not have clusters in any unique areas; that is, he did not have clusters in any areas in which no other control participant had a cluster. With regard to the right hemisphere, there were no areas in which at least 6/8 participants exhibited significant clusters. However, it is worth noting that DPT exhibited significant activation in the right fusiform, as did four of the control participants, suggesting that DPT's activation in this area, while not the "normal pattern" was certainly not unique or abnormal. However, while DPT's activation cluster was in the posterior portion of the right fusiform (Talairach coordinates: 39 −67 −20), the four control participants had significant clusters in the mid fusiform region (y= −34 to −55).

In terms of peak voxel intensities, there were no significant differences between DPT and control participants for any of the regions reported in Table 5 (Crawford and Garthwaite modified t-test values ranging from −.65 to .90).

The Mahalanobis distance statistic comparing DPT to the control participants was computed for the 4 left hemisphere regions where at least 6/8 controls showed significant activation. The analysis revealed that the location of DPT's clusters were normal in all areas except for the fusiform. In particular, DPT's activations in the Left IPS, Left IFG, and Left STG did not differ from those of the control participants ($MD^2_{L\ IPS}$= 2.18, p = 0.54; $MD^2_{L\ IFG}$=2.1, p=0.55; $MD^2_{L\ STG}$ =3.12, p=0.37, respectively). With regard to the left fusiform, DPT had two activation peaks. The peak in the mid fusiform was within normal range ($M_{FG\ Mf}$=4.15, p = .25) while the peak in the posterior fusiform fell outside the normal range ($M_{FG\ Pf}$=12.9, p = .0001). Figure 6 depicts the location of the peak activations for DPT and control participants in the left fusiform, along with the Mahalanobis-computed 95% confidence interval (shaded ellipse). Furthermore, the difference in activation locations between DPT and individual control subjects identified in the Mahalanbis analysis is consistent with the group results as identified in the random effects analysis. This can be seen in Figure 7, which depicts both the group and DPT's fusiform activations. However, as can be seen in Table 5, for the left fusiform region, there were two clusters (for Subjects 7 and 8) whose peaks were quite anterior (and inferior) relative to the others. To evaluate whether or not these two clusters were responsible for the difference between DPT and the controls, we carried out another Mahalanabois analysis excluding one or both of these peaks. In either case DPT's peak location remained significantly different from the controls ($M_{FG\ Pf}$=14.73, p = .0001 and $M_{FG\ Pf}$=28.98, p = .0001).

5.4.3. Results: Silent reading of words—The random effects group analysis revealed activation in the following areas for the words > checkerboard contrast in the control group: left fusiform gyrus, left inferior temporal gyrus, bilateral pre-central gyrus, left superior temporal gyrus, bilateral intraparietal sulcus, and bilateral inferior frontal gyrus. Figure 3 specifically depicts (in orange) the group activation for words>checkerboards in the

fusiform. As can be seen, it overlaps with the pseudowords > checkerboards cluster and also falls within DPT's lesion area.

For the individual subject analyses, the areas that were activated by at least 6/8 controls are reported in Table 6; in addition, the table also lists the one area that was uniquely activated by DPT. With regard to peak voxel intensities, there were no significant differences between DPT and control participants for any of the areas reported in Table 6 (Crawford and Garthwaite modified t-test values ranged from −.58 to.08).

The similarities and differences between the activation topographies for word reading for DPT compared to control participants are as follows: (1) Left IPS: both normal controls and DPT exhibited significant activation in this area and Mahalanobis distance statistics indicate that the location of DPT's peak activation in this area was not different than for controls (MD^2=3.1, p = .38). (2) Left IFG: DPT did not exhibit significant activation in the left IFG, although 6/8 controls did and despite the fact that he did activate this area in reading pseudowords. Activation was absent in this region for DPT even when a range of thresholds (p=.00005, .005, .001, .01) were examined. However it is worth remembering that two control participants also did not activate this area. (3) Left and right anterior temporal lobe (ATL) (Middle Temporal Gyrus): Robust activation was observed for DPT although these areas were not activated for any of the control participants even when a range of thresholds (p=.00005, .005, .001, .01) was examined. (4) Left and right fusiform: DPT exhibited activations in both right and left fusiform gyri as did at least 6/8 control participants. As indicated in Figure 8, Mahalanobis statistics revealed that DPT's activation cluster for the left fusiform was significantly outside the normal range (MD^2=27.66, p=.000). For the right fusiform, DPT exhibited an activation peak in the posterior fusiform, that was highly similar to what was observed in pseudoword reading (Figure 8) Mahalanobis analysis revealed that the location of this right fusiform cluster was outside the normal range (MD^2=13.45, p=. 004). The findings of the Mahalanobis analysis are also consistent with the results of the random effects group analysis. This can be seen in Figure 9 in which the fusiform activations for the group are depicted along with DPT's. (5) Finally, we note that DPT activated both left and right inferior/middle occipital gyri, and while this was not a pattern exhibited by the majority of normal controls, 4/8 controls also activated this region; therefore, DPT's activation cannot be considered anomalous.

Since the right and left hemisphere ATL (anterior temporal lobe) activations were strikingly unique to DPT we carried out an additional VOI analysis to examine their response characteristics in greater detail. Specifically, we contrasted the %BOLD signal change for words compared pseudowords in these two clusters. The results of this analysis revealed that the ATL clusters were significantly more activated for words than pseudowords (t=2.1, p=. 04 for the left hemisphere ATL; t= 2.24, p=.02 for the right hemisphere ATL). The cluster sizes for the left and right ATL clusters were 614 and 1822 mm^3, respectively. (Note, these clusters are only partially visible in Figure 9)

6. General Discussion

In this investigation of functional neural reorganization, we considered an individual (DPT) with a resection lesion affecting the left mid-fusiform/inferior temporal gyrus. Wwe examined the relationship between DPT's behavioral and neural response patterns for faces, objects, written words and pseudowords, and also used a systematic approach for comparing DPT's activations with those of normal controls. For the latter, we used a novel application of an existing method (Mahalanobis) that allowed for a statistical evaluation of the degree to which the location of DPT's peak activations were abnormal or not.

Summarizing, the primary findings of this study are: (1) Face and object processing were within normal range both behaviorally and neurally; (2) Pseudoword reading was normal behaviorally, and was largely supported by activations in areas that were observed in normal controls: left hemisphere inferior frontal gyrus (IFG), intra-parietal sulcus (IPS), superior termporal gyrus (STG) and the left fusiform gyrus (FF) as well as the right hemisphere FF. However, both left and right hemisphere FF activations were shown to be displaced relative to normal; (3) Word reading was abnormal behaviorally, with a pattern that indicated an impairment in translating between orthographic word forms and word meaning (both in reading and spelling). Word reading yielded activations in areas also observed in normal controls, namely in the left hemisphere IPS and left and right hemisphere FF gyri. However, three major abnormalities were noted. First, as for pseudowords, both left and right fusiform activations were displaced relative to normal. Second, there was no left IFG activation (observed in 6/8 controls) and, third, significant activation clusters were observed bilaterally in the anterior temporal lobes (specifically, the anterior middle temporal gyri) and these were not observed in any of the control participants.

6.1. Patterns of response to neural injury

DPT exhibited the three types of response to neural injury that were identified in the Introduction. In this section we discuss the implications of these findings for our understanding of the neural substrates that support the processing of each stimulus type and mechanisms of functional reorganization. Before proceeding, an important caveat must be clearly stated, and that is that the specificity and strength of the interpretations are necessarily dependent upon the “granularity” of the cognitive and neural measures. That is, it is always possible that what appear to be normal behavioral and/or neural outcomes could be shown to be abnormal if more fine-grained (or different) measurements or analyses were employed. This is the case for this investigation but, necessarily, will be true of any investigation of this type. It is also worth noting the possibility that the etiology of a lesion may influence the specific pattern of reorganization. DPT suffered from a slow-growing tumor which could have prompted some reorganization and then he underwent surgical removal of the tumor area which could have prompted additional changes. Only with the development of a database of detailed studies of individuals with different deficit etiologies will we be able to understand the possible role of etiology in patterns of functional reorganization.

For face and object processing we observed the Type 1 Pattern: Normal behavior/Normal neural response. Specifically, this indicates that the lesioned area of the left fusiform/inferior temporal gyrus is not strictly necessary for the visual processing of faces and objects. Furthermore, the neuroimaging findings indicate that it is unlikely that DPT’s normal behavioral processing of faces and objects was the result of functional reorganization because activations in these regions appeared to be normal. While this is not entirely surprising given previous results in the literature, it reinforces those findings. Additionally, the results have implications regarding the specificity of impact of neural injury. That is, although the inferior temporal lobes have been generally associated with object and face processing, the results obtained with DPT indicate that important disruptions within this larger region do not necessarily result in functional reorganization of processes that make use of nearby substrates.

For pseudoword reading we observed the *Type 2 Pattern; Normal behavior/Abnormal neural response*. The fact that there were neural differences between DPT and normal controls indicates that the lesion affected the normal substrates for this function. The fact that these neural differences were accompanied by normal behavior indicates that successful functional reorganization occurred. Presumably the normal activations observed for DPT in the IFG, IPS, STG support intact subcomponents of the complex process of pseudoword

reading. While there is no clear consensus on the specific cognitive role of these areas in pseudoword reading, it can be mentioned that the IPS activation may reflect the region's involvement in attentional control (Serences et al., 2004) and/or updating of working memory (Roth & Courtney, 2007) while the left STG recruitment is consistent with the finding that the area is involved in listening to pseudowords (Pugh et al., 1996; Simos et al., 2002). In addition, the IFG is an area that has been quite often found involved in reading and in particular the reading of pseudowords (Xu et al., 2001; Paulesu et al., 2000; Brunswick et al., 1999; and also Mechelli et al., 2003, for a review).

With a Type 2 response, it can be inferred that the neural response abnormalities are likely to be important in the successful reorganization of function. Specifically, in this case, we see bilateral abnormalities in the location of the fusiform activations. In the left hemisphere, the displacement of peak activity relative to normal controls may be understood as recruitment and reorganization within the perilesional region. This would be generally consistent with other findings of perilesional recruitment (Belin et al., 1996; Kurland et al., 2008; Saur et al., 2006; Thompson, 2008). Perilesional changes may reflect reinstantiation of function based on remnants of the damaged circuitry and recruitment of nearby substrates. Quite intriguing are the right hemisphere findings. The fact that right fusiform activation was observed is not, in and of itself, surprising as 4 controls also exhibited right fusiform activation, and it has also been reported in the literature (see Jobard et al., 2003, 2007, for reviews). It is generally believed that the right hemisphere region is unlikely to play a necessary role in normal pseudoword reading, though may be available to be recruited in case of damage (Hillis, 2004). What is unexpected is that the right hemisphere cluster is located more posteriorly than the fusiform clusters observed in the normal controls, whose clusters appeared in the mid-fusiform region. Why should there be a posterior displacement in DPT's case, when the right mid-fusiform was intact? One possibility is that the posterior location was not truly abnormal but that we simply had limited control data (only 4/8 controls showed right FF activations). Another, more interesting possibility is that the right hemisphere shift is linked to the left hemisphere displacement. If homologous processing circuits are linked cross-hemispherically, it is possible that changes in one hemisphere (especially the dominant one for that function) could induce changes in the other. Possibly related, are findings concerning the anterior temporal lobes recently reported by Warren et al., (2009). These researchers found, based on a PET data, that local cortical dysfunction in ATL may induce remote cortical dysfunction because the mechanisms of transfer and integration of information between connected and related brain areas may be disrupted as well.

For word reading, we observed a Type 3 pattern: Abnormal behavior/Abnormal neural response. This pattern indicates that the neural injury affected substrates necessary for performing the function but that reorganization, if any, was insufficient to support normal behavioral responses. Before discussing the abnormal neural responses we should mention that DPT's exhibited neural responses in the left IPS that were consistent with those of control participants. These, presumably, reflect the intact subcomponent functions involved in reading, which were discussed just above.

In terms of anomalous neural responses, there were displacements within right and left fusiform gyri observed for word reading and, furthermore, these were extremely similar to those observed in pseudoword reading (LH: words: 42 −67 −17 and pseudowords: −42 −67 −17 and RH: words: 36 −70 −20 ; pseudowords: 39 −67 −20). Presumably these abnormalities reflect the same functional reorganization that supported normal behavioral responses in pseudoword reading. Given that these bilateral fusiform changes were insufficient to allow for normal word reading but supported normal pseudoword reading we can infer that they involved sublexical/prelexical aspects of the reading process. This would be consistent with a number of findings indicating that the more posterior aspects of the

fusiform play just such a role (e.g., Gaillard et a.l, 2006). Furthermore, posterior activation in the left lingual gyrus (−16, −79, −10) was reported in an fMRI study of an individual with acquired phonological alexia who received training designed to strengthen sublexical processing (Small et al, 1998). Importantly, these neuroimaging findings are consistent with claims of models such as the hierarchical model of reading (Dehaene et al., 2005; Vinckier et al., 2007 that posit that word recognition proceeds through areas spanning the ventral visual cortex from posterior occipital regions (TC y<−80) to relatively anterior fusiform regions (TC y= −40). Specifically, the hierarchical model proposes that 'the VWFA can be analyzed into successive regions with an increasing invariance for location and an increasing dependence of letter order, from letter detectors (around y=−64) to bigram (y=−56) and possibly morpheme detectors (y= −48)' (Gailard et al., 2006).

As we have noted, DPT exhibited significant right hemisphere fusiform activation for word reading that was not, in itself abnormal, as four of the 8 controls also exhibited activation in this general area. However, as indicated in the Introduction, recruitment of right hemisphere fusiform (and occipital) areas has been reported in the various reports of letter-by-letter reading, and the results obtained here with DPT further underscore the likely role that this region plays in the recovery/response to lesions to posterior left hemisphere areas.

A second major anomaly observed in DPT's neural responses is the absence of left IFG activation observed in 6/8 of the control participants. This is an area that has been commonly reported to be active in word reading, although there is no clear consensus regarding its function. Proposals range from claims that the IFG is associated with fine-grained, articulatory phonological recoding (Pugh et al., 2001; Fiez et al., 1998; Joubert et al., 2004; Simos et al., 2002; Vigneau et al., 2005) to claims that this area (BA 44 and 45) may support grapheme-to-phoneme conversion or even lexical search (Heim et al., 2005; Gailard et al., 2003; see also Mechelli et al., 2003 for a review). The fact that DPT does not activate this area is consistent with the behavioral data indicating abnormally slow access to meaning for printed words and significantly slower oral reading response times for low frequency and irregular words. However, we do note that 2/8 controls also did not activate this region, limiting the significance of the result.

The third major anomaly relating to DPT's neural activation pattern for words is the bilateral activation in the anterior temporal lobes, something not observed in any of the control participants (RH: 57 2 −11 and LH: −60 −1 −17). In fact, the anterior MTG is not typically reported in fMRI studies of silent reading (for reviews, see Mechelli et al., 2003; Jobard et al., 2003; Cohen et al., 2002), although in at least some MEG and PET studies it has been found to be involved in semantic processing during reading (see Patterson et al, 2007; Warren et al, 2009). Bilateral atrophy in this area has been strongly associated with semantic dementia and difficulties in processing word meanings (Crinion et al., 2003; Hodges et al., 2000; Marinkovic et al., 2003; Mummerey et al., 2002; Lambon-Ralph et al., 2002; Visser et al, 2009; Woollams et al., 2007). Also consistent with a semantic role for this region are the results reported by Kurland et al., (2008) in an fMRI study of the neural changes associated with a semantic treatment of acquired dyslexia. They found that left hemisphere ATLwas associated with the treatment effects and argued that the treatment took advantage of their client's intact semantic route such that activity in this region reflected reliance on semantic processing. Furthermore, a recent voxel-based lesion-symptom mapping study by Schwartz et al (2009) found that damage in the left anterior temporal lobe (subsequent to stroke) was associated with semantic errors in word production. On this basis, he authors argued that this region is involved in the communication between the lexicon and semantic system

Certainly the functional role of the anterior temporal lobes is not fully understood although an association with word meaning processing is quite widespread and has been observed

with various methods and in various populations. Interestingly, in DPT's case, a VOI analysis comparing activation for words versus pseudowords within the ATL clusters, revealed a greater responsiveness for words compared to pseudowords. Given that the pseudoword stimuli were phonotactically similar to the word stimuli, the primary difference between words and pseudowards was the presence or absence of meaning. Therefore, the findings of these VOI analyses, also point to the special role of the ATL in processing word meanings. This may provide an explanation for why this area was active for DPT when silently reading words but not pseudowords. We know from the behavioral study summarized in this paper and described in more detail in Tsapkini & Rapp (2010) that DPT's semantic representations themselves were intact and readily accessed from auditory words or pictures. His difficulty quite specifically concerned gaining access to meaning from orthographic word forms in reading (and vice versa in spelling). Thus the anomalous bilateral ATL activation could represent an attempt to use meaning in a greater-than-normal, top-down manner to assist in word reading. If so, activations in this area could be considered to be compensatory (albeit insufficient) mechanisms recruited to circumvent and/or cope with a deficit. Various other interpretations are, of course, possible.

6.2. Conclusions

There is widespread interest in understanding how the brain responds to and reorganizes after damage, as such an understanding has implications for both basic neuroscience and clinical practice. Functional neuroimaging methods provide today a unique opportunity to 'observe' this reorganization while it is taking place in the living brain. In this study we have illustrated how the consideration of neural responses patterns and their relationship to well-described patterns of spared and impaired cognitive functions can shed some light on these issues. At a theoretical level we have laid out the different types of neural response to brain injury that one may expect to find, illustrating them with examples from this investigation. At a methodological level, we have demonstrated how a novel application of Mahalanobis distance analyses can be used to compare single cases to a group of individual controls. Finally, we have described specific perilesional, contralesional and ipsilesional changes in neural responsiveness that can occur subsequent to damage to left fusiform and inferior temporal areas involved in written language processing. With this work we hope to have contributed to the ongoing effort to disentangle the enormously complex puzzle of brain reorganization.

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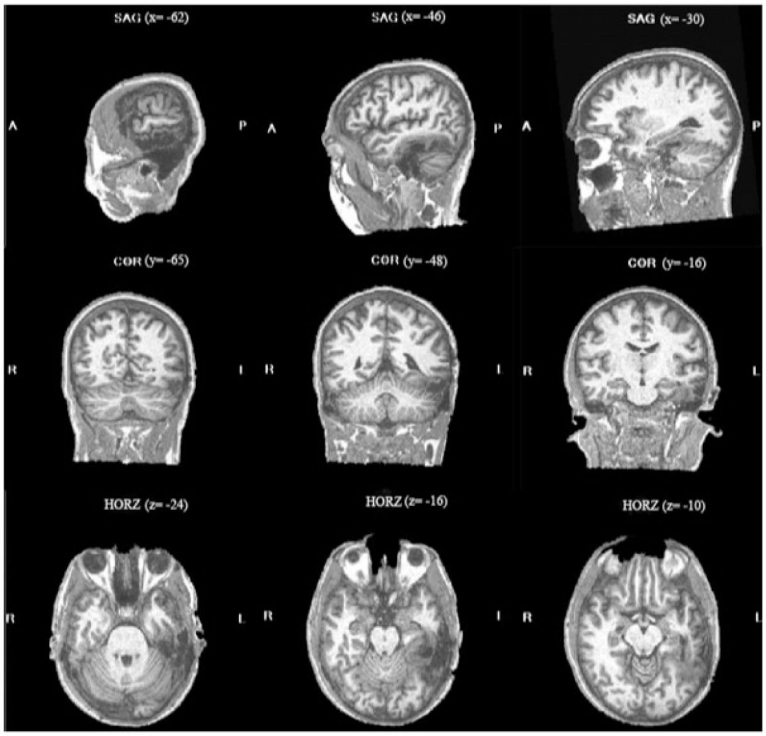

Figure 1.
Sagittal, coronal and horizontal MRI images showing the lateral-medial(x=−62 to −30), posterior-anterior (y= −65 to −16), and inferior-superior edges (z= −24 to −10) and midpoints of DPT's resection lesion.

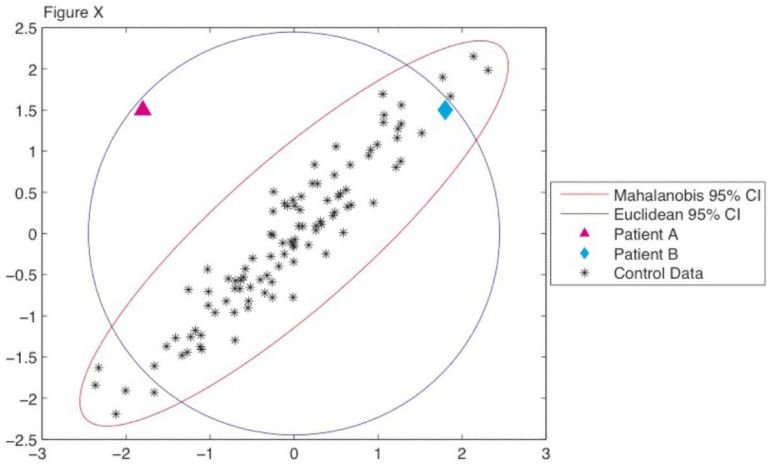

Figure 2.

Depiction of difference between Euclidean and Mahalanobis distance for a sample of 100 randomly generated two-dimensional data points (depicted with black asterisks) with a mean of 0,0 and a covariance of [1,.95;.8,1]. The blue circle depicts a 95% confidence interval for euclidean distances centered around the mean. The red ellipsoid depicts a 95% confidence interval for mahalanobis distances centered around the mean. The magenta-colored triangle is the data point generated for Patient A and the cyan-colored diamond is the data point generated for patient B. Based on Euclidean distance Patients A and B are exactly the same distance from the group, mean but with Mahalanobis distance Patient A is considered much further away from the mean than Patient B. This figure provides an example of how Mahalanobis distance is sensitive to the distributions of individual values along multiple dimensions whereas Euclidean distance is not.

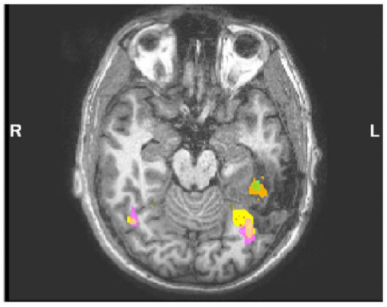

Figure 3.
Fusiform activations for the control group, reported on a horizontal image from DPT's structural MRI. This allows for localization of normal activations relative to the lesioned substrates. Activations are depicted for the following contrasts FACES>scrambled faces (pink), OBJECTS>scrambled objects (yellow), PSEUDOWORDS>checkerboards green) and WORDS>checkerboards (orange). See text for details regarding the various analyses.

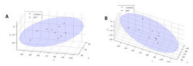

Figure 4.
Mahalanobis distance plot of peak activations for DPT and control participants for significant clusters obtained in the contrast FACES> scrambled faces for the (a) left and (b) right fusiform gyri. The ellipsoid represents the 95% confidence interval and x, y, and z represent dimensions in Talairach coordinate space.

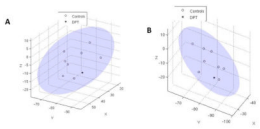

Figure 5.
Mahalanobis distance plot of peak activations for DPT and control participants for significant clusters obtained in the contrast OBJECTS> scrambled objects for the (a) left and (b) right fusiform gyri. The ellipsoid represents the 95% confidence interval and x, y, and z represent dimensions in Talairach coordinate space.

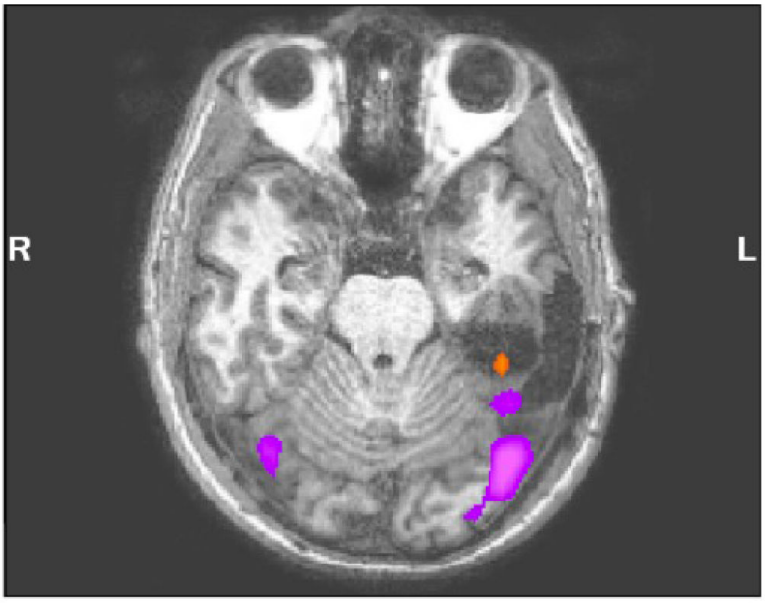

Figure 6.
Fusiform activations are reported for the PSEUDOWORDS>checkerboards contrast, for DPT (purple) and the control group (orange), depicted on a horizontal image from DPT's structural MRI. See text for analysis details.

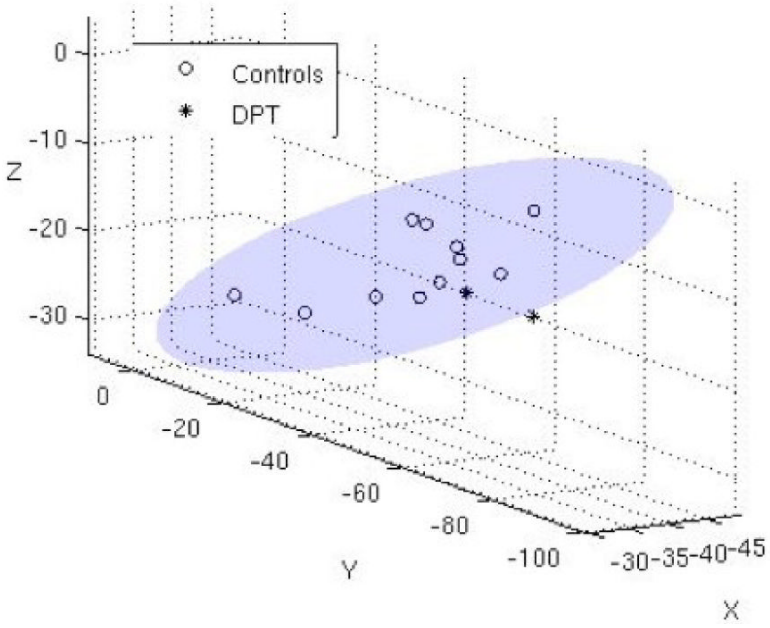

Figure 7.
Mahalanobis distance plot of peak activations for DPT and control participants for significant clusters obtained in the contrast PSEUDOWORDS>checkerboard for the left fusiform gyrus. The ellipsoid represents the 95% confidence interval and x, y, and z represent dimensions in Talairach coordinate space.

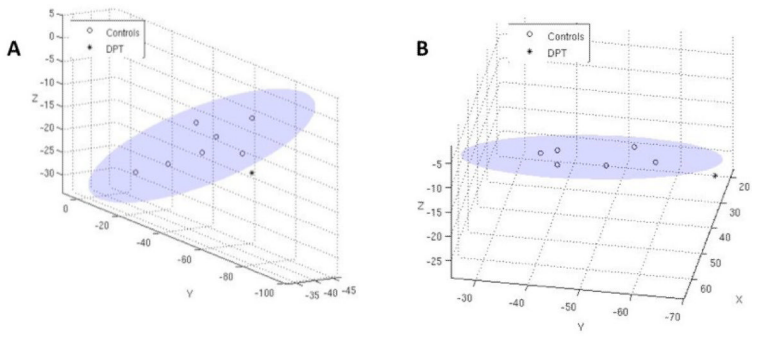

Figure 8.

Mahalanobis distance plot of peak activations for DPT and control participants for significant clusters obtained in the contrast WORDS> checkerboard for the (a) left and (b) right fusiform gyri. The ellipsoid represents the 95% confidence interval and x, y, and z represent dimensions in the Talairach coordinate space.

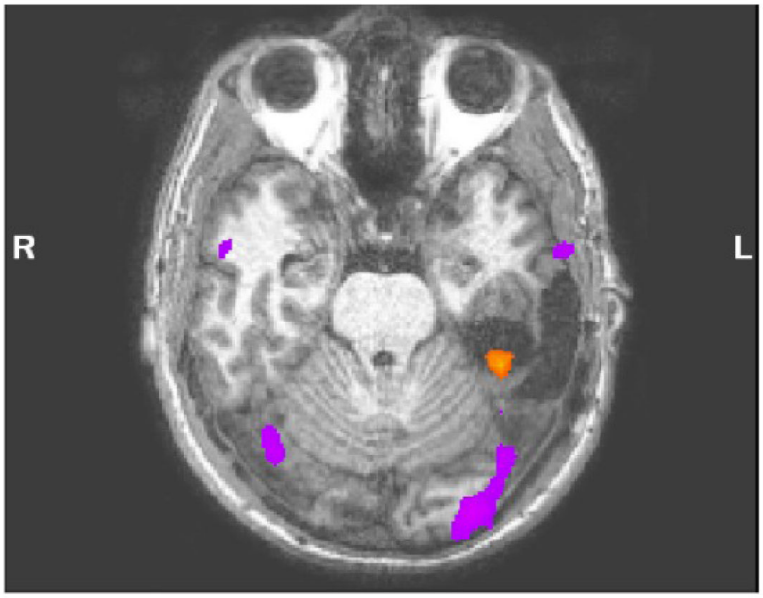

Figure 9.
Fusiform activations are reported for the WORDS>checkerboards contrast, for DPT (purple) and the control group (orange), depicted on a horizontal image from DPT's structural MRI. See text for analysis details.

Table 1

Summary of behavioral testing reported in Tsapkini & Rapp (2010). Median RTs and means of medians are reported in milliseconds. Pyramids and Palm Trees (Howard & Patterson, 1992). Statistical comparisons were carried out using the Crawford & Garthwaite (2002) modified t-test.

.TASK	DPT	CONTROLS MEAN (RANGE) (SD)	STATISTICAL COMPARISON DPT VS. CONTROLS
Spelling			
Words	81% (55/68)	96% - 100% (0-3/68)	p<.05
Pseudowords	97% (33/34)		
Pseudoword reading	759	582 (465-804) (117)	ns
Word Reading			
High frequency			
Low frequency	583	470 (388-596) (62)	ns
Regular	615	477 (398-617) (65)	p<.1
Exception	588	475 (391-608) (64)	ns
	632	477 (393-614) (63)	p<.05
Visual Lexical Decision			
High frequency			
Low frequency	675	572 (465-766) (91)	ns
Reg/consistent	807	640 (537-809) (84)	p<.1
Reg/inconsistent	718	602 (490-767) (89)	ns
Strange	712	574(535-801) (82)	ns
	727	597 (484-767) (86)	ns
Synonym judgment			
Written	976	762 (564-965) (105)	p<.1
Auditory	1382	1036 (719-1456) (248)	ns
Visual Lexical Decision and Semantic Priming			
Lexical decision	698	633 (486-880) (128)	ns
Priming effect: unrelated-related	12	43 (29-73) (18)	p<.05
Spoken Picture Naming			
High frequency	822	687 (579-881; 116)	ns
Low frequency	1035	788 (683-932; 128)	ns
High complexity	1098	806 (681-915; 122)	ns
Low complexity	1140	817 (654-1059; 164)	ns
Auditory semantic priming			
Overall Lexical Decision	1183	1101 (964-1363; 150)	ns

.TASK	DPT	CONTROLS MEAN (RANGE) (SD)	STATISTICAL COMPARISON DPT VS. CONTROLS
Priming effect: unrelated-related	169	200 (152-283; 46)	ns
Faces: Fame judgment	1183	938 (772-1434; 235)	ns
Faces: Occupation categorization	838	823 (523-1123; 163)	ns
Object comprehension: Pyramid and Palm Trees (timed)	2269	1765 (1147-2565; 504)	ns

Table 2

For the contrast FACES > scrambled images, the locations and t-values for the activation peaks of clusters in the fusiform/occipital gyri. Data for controls subjects and DPT are reported. (Bonferroni correction (brain-wise) for multiple comparisons ($p<.05$). Talairach coordinates are reported (Talairach & Tournoux, 1988).

Subjects	L. Fusiform/Occipital gyri	t-value	R. Fusiform/occipital gyri	t-value
S1	−33 −88 −2	24.7	36 −82 −2	23.2
S2	−39 −58 −17	17.1	36 −49 −14	17.1
S3	−33 −85 −17	23.6	39 −79 −17	23.2
S4	−33 −46 −11	14.1	36 −61 −11	20.1
S5	−30 −88 −20	19.5	36 −67 −11	23.3
	−45 −61 1	8.5		
S6	−33 −88 −8	16.5	45 −73 −11	15.8
S7	−30 −76 −14	20.6	39 −76 −20	26.7
S8	−33 −79 −2	21.2	60 −46 −17	5.7
			48 −79 −2	21.1
DPT	**−36 −82 −20**	**24.4**	**27 −82 −17**	**28.9**

Table 3

For the contrast OBJECTS > scrambled images, the locations and t-values for the activation peaks of clusters in the fusiform/occipital gyri. Data for controls subjects and DPT are reported. (Bonferroni correction (brain-wise) for multiple comparisons ($p<.05$). Talairach coordinates are reported (Talairach & Tournoux, 1988).

Subjects	Left Fusiform/ Occipital gyri	t-value	Right Fusiform/ Occipital Gyri	t-value
S1	−33 −82 1	26.1	36 −82 −2	26.2
S2	−36 −76 −11	19.2	27 −82 1	18.4
S3	−36 −88 −11	17.1	51 −79 −11	14.8
S4	−39 −67 −5	18.5	39 −73 −8	19.7
S5	−36 −85 −20	17.6	36 −73 −11	17.3
S6	−30 −88 −5	19.4	30 −91 −5	22.3
S7	−30 −76 −14	25.7	39 −79 −17	24.7
S8	−30 −79 4	20.5	45 −76 1	20.1
DPT	**−36 −82 −20**	**28.3**	**30 −79 −17**	**26.9**

Table 4

For the contrast FACES > objects, the locations and t-values for the activation peaks of clusters in the fusiform/occipital gyri. Data for controls subjects and DPT are reported (cluster size correction for multiple comparison with voxel-wise threshold of p <.0001, corrected p<.05).Talairach coordinates are reported (Talairach & Tournoux, 1988).

Subjects	Left Fusiform/ Occipital Gyri	t-values	Right Fusiform/ Occipital Gyri	t-values
S1	−42 −34 −11	5.9	42 −55 −17	5.6
			60 −25 −29	10.6
S2	−39 −43 −17	8.1	39 −40 −14	8.3
			45 −55 1	6.9
S3	−36 −88 −20	9.7	39 −52 −23	13.5
	−42 −25 −23	4.5	57 −61 −2	9.8
	−51 −43 −5	7.5		
S4	−45 −49 1	5.0	39 −37 −11	9.3
			36 −61 −14	6.5
S5			36 −55 −20	10.4
S6	−54 −40 −2	6.5	60 −52 1	13.7
S7	−36 −61 −2	5.0	45 −31 −20	4.8
			45 −58 −17	5.3
			54 −61 −2	7.7
S8	−36 −49 −11	5.9	42 −40 −14	5.0
			54 −22 −26	5.0
			36 −64 −2	7.3
			45 −58 −26	4.6
DPT	**−39 −67 −23**	**7.6**	**45 −52 −2**	**16.3**

Table 5

For the contrast PSEUDOWORDS > checkerboards, the locations and t-values for the activation peaks of clusters in neuroanatomical regions in which at least 6/8 control subjects showed significant effects. Data for controls subjects and DPT are reported. Bonferroni correction (brain-wise) for multiple comparisons (p<.05). Talairach coordinates are reported (Talairach & Tournoux, 1988).L= left hemisphere; IPS=intraparietal sulcus; IFG=inferior frontal gyrus; STG=superior temporal gyrus; ITG=inferior temporal gyrus.

Subjects	L IPS	t-value	L IFG	t-value	L STG	t-value	L FUSIFORM/ITG	t-value
S1	−36 −46 40	5.8	−54 14 10	7.0	−57 −28 4	7.9	−42 −67 −5	7.0
							−42 −43 −11	6.9
S2	−21 −67 37	6.7	−33 26 22	6.3			−36 −61 −11	6.2
							−42 −40 −11	6.9
S3	−27 −73 43	11.9	−48 2 16	14.4	−54 −52 2	6.5	−42 −46 −17	14.3
	−57 −28 16	11.1						
S4	−24 −61 52	13.3	−48 8 34	12.2	−51 −40 4	6.2	−39 −55 −11	13.7
S5			−30 20 7	6.1			−36 −52 −17	6.6
S6	−21 −64 40	7.0	−57 17 19	8.8	−48 −40 −2	6.3	−39 −37 −20	7.6
	−30 −46 43	6.8			−51 23 −14	5.9		
					−60 −31 16	5.5		
S7	−21 −76 19	15.6			−42 −49 7	9.5	−36 −70 −11	13.9
	−54 −34 40	6.3			−51 −28 −5	5.8	−33 −16 −23	7.9
S8	−54 −49 34	5.5			−63 −52 1	6.2	−42 −16 −26	6.4
DPT	**−27 −73 37**	**9.9**	**−33 20 7**	**6.9**	**−54 −22 10**	**6.1**	**−42 −52 −17**	**6.5**
							−42 −67 −17	**9.3**

Table 6

For the contrast WORDS > checkerboards, the locations and t-values for the activation peaks of clusters in neuroanatomical regions in which at least 6/8 control subjects showed significant effects, or DPT uniquely showed an effects. Cluster-size correction for multiple comparisons was applied (uncorrected voxelwise p< .0001; corrected p<.05). Talairach coordinates are reported (Talairach & Tournoux, 1988). L= left hemisphere; IPS=intra-parietal sulcus, MTG= middle temporal gyrus, ITG inferior temporal gyrus

Subjects	L IPS	t-value	L IFG	t-value	L MTG	t-value	L FUSIFORM/ITG	t-value	R MTG	t-value	R FUSIFORM	t-value
S1	−33 −46 37	5.4	−51 20 22	7.0			−42 −67 −5	9.0			54 −43 −11	5.0
S2							−42 −40 −11	6.5				
S3	−21 −73 40	6.8	−48 29 4	7.8			−42 −43 −17	11.0			36 −49 −20	6.8
S4	−27 −61 49 −24 −73 25	13.1 5.9	−48 11 34	11.4			−39 −55 −11	14.8			54 −43 −8	5.8
S5											33 −58 −20	5.2
S6	−21 −64 40	8.5	−57 20 16	12.0			−36 −37 −20	10.0			39 −55 −14	11.5
S7	−18 −55 43	8.1	−39 −10 43	8.7			−36 −73 −11	10.7			39 −37 −17	5.0
S8	−21 −52 37	5.2	−39 26 19	5.1			−39 −16 −26	4.4				
DPT	**−27 −73 37**	**7.8**	**None**		**−60 −1 −17**	**6.1**	**−42 −67 −17**	**7.4**	**57 2 −11**	**5.2**	**36 −70 −20**	**5.6**