Is left fronto-temporal connectivity essential for syntax? Effective connectivity, tractography and performance in left-hemisphere damaged patients

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ABSTRACT

Syntactic processing typically engages left inferior frontal gyrus and posterior middle temporal gyrus, and damage to these regions is associated with syntactic deficits. What has not been directly determined, however, is whether it is the effective connectivity between these regions – and therefore also the integrity of the white matter tracts that connect them – that underpins successful syntactic analysis. We addressed these related issues by obtaining measures of the psycho-physiological interaction between frontal and temporal regions and of the integrity of the major white matter tracts that directly connect them — the arcuate fasciculus and extreme capsule fibre system. We correlated these estimates with performance measures of syntax in a group of patients with left hemisphere damage and varying degrees of syntactic impairment. Good syntactic function was associated with enhanced effective connectivity and increased tract integrity, suggesting that intact connectivity between left frontal and temporal regions is essential for syntactic analysis rather than the activation of these regions *per se*.

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Introduction

Neuropsychological studies of patients with syntactic impairments have shown that damage to the left inferior frontal gyrus (LIFG) is frequently associated with syntactic deficits, whereas damage to homologous RH regions has little impact on syntactic processing (Dronkers et al., 2004; Ludlow et al., 1986). These findings suggest that the LIFG plays a key role in syntactic processing. However, it is clear that integrity of the LIFG is not the only requirement for successful syntactic processing, since damage to other brain regions – most notably the left posterior middle temporal gyrus (LpMTG) – has also been shown to disrupt syntactic analysis (Caplan et al., 1996; Dronkers et al., 2004; Tyler and Marslen-Wilson, 2008; Tyler et al., 2011). Studies with healthy populations have also highlighted the importance of the LIFG in syntactic processing (Caplan et al., 1999, 2000), as well as co-activation of LIFG and LpMTG (Caplan et al., 2008; Dapretto and Bookheimer, 1999; Keller et al., 2001; Rodd et al., 2010; Tyler and Marslen-Wilson, 2008; Tyler et al., 2010, 2011). These results show that both these regions are involved in syntactic analysis and that they are jointly essential for syntactic function, suggesting that they must be strongly functionally connected.

The anatomical underpinnings of this connectivity have been recently revealed by tractography analyses which show that LIFG and LpMTG (and their RH homologues) are connected via major white matter tracts — dorsally via the arcuate fasciculus (AF; Catani et al., 2005; Glasser and Rilling, 2008) and ventrally via the extreme capsule fibre system (ECFS; Makris and Pandya, 2009). These are thought to be the main tracts which directly connect LIFG and LMTG (and LSTG), they are associated with language processing (Friederici, 2009; Saur et al., 2008), and recent work suggests that the integrity of both may be necessary for syntactic comprehension (Griffiths et al., 2009). If the integrity of the tracts connecting frontal and temporal regions is associated with effective connectivity between those regions in the context of preserved syntactic function, then any reduction in fronto-temporal effective connectivity and in tract integrity should lead to syntactic deficits.

To address these predictions, we obtained estimates of effective connectivity in both healthy controls and patients with acquired LH brain damage. The control group data provide a baseline measure of fronto-temporal connectivity in the context of syntactic processing in the healthy system. Including patients in the study enables us to ask whether intact functional and structural connectivity is essential for syntactic processing, since the patients formed a heterogeneous group. Unlike the controls, who all had intact syntax, patients varied in their syntactic processing abilities and in the location and extent of their lesion within the LH. This variation enabled us to relate syntactic performance to modulation of connectivity to determine whether it is

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essential for intact syntactic performance (Chatterjee, 2005; Price et al., 2006; Tyler et al., 2011). We predict that if LH fronto-temporal connectivity is essential for syntactic analysis, then the extent to which it is disrupted in individual patients will correlate with their syntactic deficits.

We obtained seeds for the effective connectivity analysis from an fMRI study of syntactic processing in which the controls and patients listened to spoken sentences in which we had manipulated syntactic ambiguity (Tyler et al., 2011). We included syntactically ambiguous sentences [e.g. *John knew that BORING COLLEAGUES…*] and unambiguous sentences [e.g. *John knew that GAMBLING GANGSTERS…*]. The ambiguous phrases had two possible syntactic interpretations, one of which was highly preferred [the dominant reading: … *were approaching his office*] and the other of which was plausible and grammatical but only had a weak preference [the subordinate reading: … *was damaging his career*]. The ambiguity was resolved by the word immediately following the phrase (WAS or WERE in the examples). We assume that listeners process spoken sentences by accessing the semantic and syntactic properties of each word as it is heard, and integrating this information into the developing sentential representation (MacDonald et al., 1994; Marslen-Wilson and Tyler, 1975, 1980). When they encounter syntactically ambiguous phrases, both readings are activated with the dominant/preferred reading being activated most strongly (MacDonald et al., 1994; McRae et al., 1998). When the upcoming speech input is inconsistent with the dominant interpretation (at the disambiguating word), the sentential representation is revised. This re-interpretation is reflected in slower and more errorful behavioural responses for subordinate compared to dominant sentences (Tyler and Marslen-Wilson, 1977; Tyler et al., 2011), and greater activation for subordinate compared to dominant sentences in the LIFG (BA 45/47) and LpMTG (Rodd et al., 2010; Tyler et al., 2011). These regions are consistently activated by various syntactic manipulations in other studies (Caplan et al., 2008; Dapretto and Bookheimer, 1999; Keller et al., 2001; Rodd et al., 2010; Tyler and Marslen-Wilson, 2008; Tyler et al., 2010, 2011), and damage to these regions is associated with syntactic deficits (Caplan et al., 2008; Dronkers et al., 2004; Tyler and Marslen-Wilson, 2008; Tyler et al., 2010, 2011). This suggests that syntactic ambiguity – particularly the effects of differences in preference strength – is a suitable means for eliciting measures of syntactic processing that will allow us to examine how coupling between the LIFG and LMTG changes as a function of syntactic processing ability in LH damaged patients.

Following the approach developed by Friston et al. (1997) we measured effective connectivity in terms of psycho-physiological interactions (PPI), defining two seeds in the LIFG (BA45/47) and LpMTG based on the healthy control group results for the syntactic manipulation (subordinate vs. dominant contrast; Tyler et al., 2011). In the first instance, we carried out effective connectivity analyses on the controls to establish the network involved in syntactic processing in the intact system. We then asked the question whether the connections identified in the intact system are essential for syntactic processing taking advantage of the variation in syntactic impairment within the patient group. For this purpose we related connectivity strength and syntactic processing ability by including individual behavioural performance measures as a regressor at the group-level analysis (Passamonti et al., 2008). We predicted that if LH fronto-temporal connectivity is indeed essential for syntactic processing, then connectivity strength will correlate positively with syntactic processing ability.

In addition, we used Diffusion Tensor Imaging (DTI) to estimate the structural integrity of the two white matter bundles known to directly connect the LIFG and LMTG and thought to be relevant for language function – the arcuate fasciculus and extreme capsule fibre system (ECFS) – for each participant. We were interested in asking the question whether damage to any of these tracts correlates with syntactic processing ability and for this purpose used the variability in syntactic ability within the patient group and correlated measures of

structural connectivity with measures of syntactic processing ability. If these tracts provide the anatomical basis for effective fronto-temporal connectivity, then comparable to the relationship between effective connectivity and behaviour, reduction in their structural integrity should be associated with increasing syntactic impairment. Moreover, if syntactic deficits are associated with reduced effective LH fronto-temporal connectivity and reduced tract integrity, then variation in the integrity of the tracts connecting frontal and temporal regions should also be associated with variation in the effective connectivity between those regions.

Materials and methods

Participants

The patient group consisted of fourteen native British English speakers (3 females) aged 35–77 (mean = 56 ± 12) with acquired brain damage restricted to the LH. All patients were stable at the time of testing, between 2 and 40 years post-stroke (mean = 8 ± 9), and were right-handed prior to the stroke. The control group included 15 healthy, native British English speakers (8 females) aged 46–74 years (mean = 58 ± 11). All participants gave informed consent prior to participation (Suffolk (now Essex 2) Research Ethics Committee). They were all tested within the last two years, were right-handed with no history of neurological illness or head injury and free of psychiatric illness or psychoactive medication for at least one year prior to scanning. No participant (patients and controls) had audiometer measurements that indicated severe hearing impairment (hearing threshold >70 dB based on guidelines published by the British Society of Audiology) or were cognitively impaired (25 or higher on MMSE and/or 26 or higher on Ravens Coloured Progressive Matrices). Patients were not selected on the basis of their language abilities or deficits. The only requirement was that their lesion was restricted to the LH. Across patients, lesions extended widely around the sylvian fissure. A lesion frequency map (Fig. 1) shows the extent and variability of lesion location across the patient group. As the figure shows, the damage is widely distributed and variable within the LH, with 81% of the total lesion volume being common to only 5 patients or less. The maximum lesion overlap involves 11 out of 14 patients and covers an area that adds up to only 0.5% of the total lesion volume.

A series of background language tests probing phonology (phonological discrimination), semantics (semantic categorisation and lexical
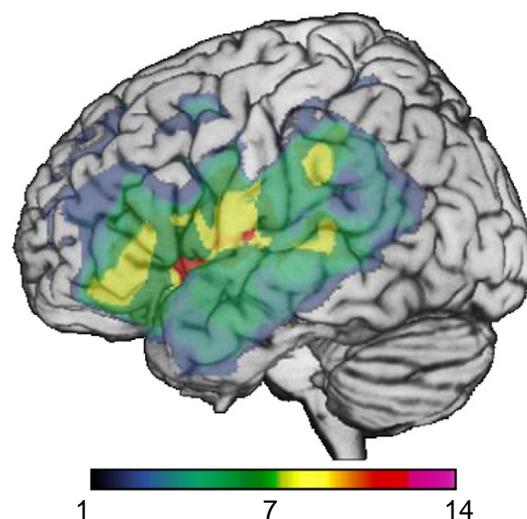

Fig. 1. Lesion frequency map. The distribution of brain damage across the patient group. The colourbar indicates the number of patients with damage at each voxel.

decision) and syntax (sentence grammaticality and sentence-picture matching) provided a set of measures describing each patient's language abilities (for additional details, see Tyler et al., 2011). These tests established that most of the patients were able to process the phonology and semantics of words without difficulty but varied in the extent to which syntactic performance was impaired. The patients' variability in syntactic processing abilities is shown across a variety of tests of syntax: in a sentence grammaticality test, patients' percent errors ranged between 0 and 42% (mean (SD) for patients = 16%(15%); for controls = 3%(3%)), and in a sentence-picture matching test (Ostrin and Tyler, 1995) the percent of syntactic errors ranged between 0 and 47% (mean (SD) for patients = 16%(15%); for controls = 4%(3%)), in strong contrast to the small number of semantic errors (mean (SD) for patients = 2%(2%); for controls = 0%(0%)). Performance on the tests of syntax (sentence-picture matching and grammaticality judgements) were significantly correlated (r = 0.57, p = 0.044). The language test scores show that none of the patients had a semantic processing deficit and that their sentence processing deficits were specific to syntax. Details of the performance of the individual patients on the behavioural tasks are presented in Tyler et al., 2011, where we present the results from the fMRI subtractive analysis for the same groups of patients and controls.

Stimuli used in the fMRI study

Effective connectivity analyses were performed on data from a study (Tyler et al., 2011) in which listeners heard sentences [n = 42] containing ambiguous phrases of the form [verb + ing noun + plural], e.g. "hunting eagles", where either the verb or the noun can be the head of the phrase depending on the sentence continuation. For example, in the sentence "Not surprisingly HUNTING EAGLES _are_ spotted over mountains", the noun "eagles" is the head of the phrase, whereas the participle "hunting" modifies the noun. However, the same phrase can also appear in a different context, where the gerund "hunting" is the head of the phrase and the noun "eagles" its object, e.g. "Not surprisingly HUNTING EAGLES _is_ banned across Europe". Both interpretations are grammatical and acceptable up to the presentation of the main verb in the sentence (in this case "is" or "are"), which occurs immediately after the offset of the ambiguous phrase and which forces the disambiguation of the phrase in favour of one or the other interpretation. Even though both interpretations of the ambiguous phrase are acceptable, listeners have a preference for one interpretation (dominant) over the other (subordinate). When the ambiguous phrase is followed by a continuation that is inconsistent with its dominant interpretation, this interpretation is revised in favour of the alternative one (subordinate). We obtained preference scores for the ambiguous phrases from a pre-test (see Tyler et al., 2011 for further details).

In addition to the ambiguous items we included 42 sentences matched in syntactic structure to the ambiguous sentences, but in which the phrase [verb + ing noun + plural] was unambiguous (e.g. "Not surprisingly QUARRELLING SISTERS _are_ sent to bed"), 126 filler sentences which did not include the phrase [verb + ing noun + plural] were also included to avoid participants becoming aware of the syntactic manipulations. We also included 42 baseline items consisting of acoustic stimuli which were constructed to share the complex auditory properties of speech without triggering phonetic interpretation (Uppenkamp et al., 2006). Baseline items were included to enable us to assess whether subjects showed intact speech processing abilities (the contrast between speech and non-speech), if they did not show any sensitivity to syntax. These conditions were not used in the current PPI analyses.

Stimuli were digitally recorded by a female native speaker of British English, and presented in the scanner via MR compatible headphones in a pseudorandom order as part of an event-related design and separated into three sessions. There were equal numbers of items of each condition in each session and subordinate and dominant versions of

the ambiguous phrases were presented in separate sessions with half of the participants hearing the dominant version first, and the other half hearing the subordinate version first. Within each session, stimuli were presented in a random order, while ensuring that no more than 3 items from the same condition were presented consecutively. To improve signal power in the fMRI experiment, the interstimulus interval was jittered according to a geometric distribution with mean 3250 ms (range from 2000 to 7000 ms; Burock et al., 1998). In the fMRI experiment, participants listened to the stimuli without making an overt response in order to minimise task-related activations.

MRI acquisition

Functional, T2*-weighted echo-planar images (EPI) were acquired using a Siemens 3T Tim Trio MRI scanner (Siemens Medical Solutions, Camberley, UK) at the MRC Cognition and Brain Sciences Unit, Cambridge. A total of 1059 volumes were acquired which comprised of 32 oblique axial slices, 3 mm thick (0.75 mm inter-slice gap), angled away from the eyes with in-plane resolution of 3×3 mm^2 (FOV = 192×192 mm^2). Volume TR was 2 s, TE was 30 ms and flip angle was 78°. We also acquired T1-weighted structural images at 1 mm isotropic resolution in the sagittal plane, using an MPRAGE sequence with TR = 2250 ms, TI = 900 ms, TE = 2.99 ms and flip angle = 9°. Diffusion-weighted images were acquired in 64 directions with two averages, with TR = 6.5 s, TE = 93 ms, b = 1000 s/mm^3 and GRAPPA parallel reconstruction. Each volume consisted of 48 slices in the intercommissural plane, 2.5 mm thick with 0.5 mm gap, in-plane resolution of 1.8×1.8 mm^2 and field of view = 230×230 mm^2. MRI and DTI were acquired in the same session, unless we already had acquired a DTI dataset within the past 2 years.

Data analysis

Pre-processing

The pre-processing of the fMRI data was the same as reported in Tyler et al. (2011). Images were slice-time and movement corrected (2nd degree B-Spline interpolation), spatially normalised to the ICBM152 T1 template using unified segmentation (Ashburner and Friston, 2005) and spatially smoothed using an isotropic 8 mm FWHM Gaussian filter in SPM5 (Wellcome Institute of Imaging Neuroscience, London, UK). For patients, normalisation used a high warping regularisation value of 100 to prevent the algorithm from warping the lesion (Crinion et al., 2007; Tyler et al., 2005). For the subtraction analysis, images were included in a mass univariate analysis using the general linear model approach (Friston et al., 1994). There were 4 conditions of interest: dominant, subordinate, unambiguous and musical rain (baseline), and effects of no interest: initial sentence fragment (before the disambiguating word), filler sentences and 6 motion parameters. The ambiguous conditions (subordinate and dominance sentences) were modelled from the onset of the disambiguating word, while the unambiguous condition was modelled from the onset of the verb which followed the [verb + ing noun + plural] phrase — similar to the ambiguous sentences. Baseline items were modelled from the onset of the stimulus. Data were high-pass filtered with a cut-off frequency of 128 s and temporal autocorrelations were modelled using a first-order autoregressive model. Contrast images were generated at the single-subject level and then included in a group level analysis. Patient contrast images were lesion-masked, i.e. for each patient, voxels identified as damaged were set to zero to avoid lesion-related artefacts. Lesion masks were generated separately for each patient using an automatic procedure described in Stamatakis and Tyler (2005).

Effective connectivity analysis

Regions of interest. Effective connectivity was measured between selected regions of interest (seed ROIs) and the rest of the brain in

terms of psycho-physiological interactions (PPI; Friston et al., 1997) using SPM8. Seed ROIs in LIFG (BA47/45) and the LpMTG were selected on the basis of significantly activated clusters (at threshold level p<0.001 voxel uncorrected, p<0.05 cluster FWE-corrected) from the subtractive analyses of the control group for the contrast of subordinate vs. dominant. This contrast shows regions whose activity is modulated by disambiguation preference, with the less preferred disambiguation (subordinate) generating greater activation than the more preferred (dominant). The two selected group cluster peaks were in the LIFG (BA47; MNI: −39 30 −9) and the LpMTG (MNI: −60 −45 9). These peaks were used as points of reference to identify individual subject activation peaks within a 24 mm radius and within the boundaries of a grey matter cortical mask (created using the WFU pickatlas toolbox, version 2.4; Maldjian et al., 2003). In this manner we identified the highest activated peaks for each subject and defined a sphere around these peaks with a 6 mm radius, which was used as the seed ROIs.

The question that we ask using the effective connectivity analysis is whether left hemisphere fronto-temporal connectivity is essential for preserved syntactic processing. To address this question we use the results from the control group to establish the syntactic processing network in healthy listeners and use the patient data to determine whether connectivity within this network is essential for preserved syntactic processing. For this reason it was necessary to use the control group cluster peaks as points of reference to define individual peaks for the patient group. In this way we were able to determine whether fronto-temporal connectivity, as defined in the normal system, was compromised if patients had syntactic deficits. The search radius (24 mm around the reference peak) was large enough to ensure that reliably activated voxels in the region would be selected, despite the large variability in lesion location across the group. We also used a cortical mask to ensure that the selected seed ROIs would be restricted to grey matter and visually inspected the selected seeds to ensure that they fell within the boundaries of the frontal and temporal lobes. Thus, we were able to handle the variability in the location of activity in each patient and ensure that all subjects had activated voxels in each ROI and could be included in the analysis. The latter was important in order to perform regressions between effective connectivity estimates and syntactic processing impairment. A figure showing the overlap and distribution of the individual seed ROIs for both patients and controls is included in the Supplementary materials.

Psycho-physiological interactions. Time-course series were extracted from each seed ROI for each participant and summarised as the first principal component across all voxels within the seed ROI sphere. The time series was then adjusted with respect to the main effects of interest to partial out confounds. Vectors representing the psychological factor (the contrast subordinate vs. dominant) were then convolved with the extracted time series to create the PPI regressors (Friston et al., 1997). The PPI regressors together with the seed ROI time-series, the experimental task vector and the 6 movement parameters as effects of no interest, were then entered in a general linear model with the 3 experimental sessions modelled separately. Even though the PPIs were the main effects of interest, we included all other regressors to ensure that any significant effects were specifically related to the PPI and could not be accounted for by any other main effect or factor.

For each seed ROI and participant we created contrast images for the main effect of the PPI, which were entered into a one-sample *t*-test at the group level. The patient contrast images were lesion-masked before entering into the group analysis as described above. Because the patient group was highly variable in terms of both damage and performance, we also entered the contrast images from the patient group in a regression analysis with measures of syntactic processing ability derived from a behavioural post-test (see below). While the

one-sample *t*-test reveals the connections that are common across the group, the regression analysis allows us to establish which connections are essential for preserved syntactic processing. Results are reported at voxel-level p<0.01 and 0.001 and cluster-level p<0.05 family-wise error (FWE). Labelling of clusters in terms of anatomical landmarks and cytoarchitectonic areas was determined using the AAL toolbox (Tzourio-Mazoyer et al., 2002).

In the PPI analysis, a significant effect indicates that the contribution of the seed region on this cluster increases or decreases as a function of task. According to Friston et al. (1997) this effect can be understood in two ways: (a) the experimental factor modulates the contribution of one region on another or (b) the activity of one region modulates the responsiveness of the other region to the experimental factor. Even though PPI is a correlational approach, the bilinear term (i.e. the interaction between the seed ROI time series and the experimental factor) breaks the symmetry of the regression, which means that the modulation is directional (Stephan, 2004). However, the direction of modulation needs to be specified a priori, since the regression can potentially be interpreted both as an increase from the seed to the target region and as a decrease from the target to the seed region. The additional inclusion of PPI contrast estimates in a multiple regression model enables us to then examine the relationship between effective connectivity and behavioural performance. In our case, a positive correlation between PPI estimates and our syntactic processing ability measure in the patient group would indicate that the contribution between the seed and target region(s) is essential for preserved syntactic processing.

Behavioural measures of syntactic processing ability

In order to avoid task-related activation, which can overlap with activation related to syntactic processing — especially in the LIFG (Kaan and Swaab, 2002), subjects in the fMRI study listened to the stimuli without carrying out an explicit task (Crinion and Price, 2005; Crinion et al., 2003, 2006; Warren et al., 2009). In order to obtain behavioural measures of syntax on the same materials as subjects heard in the scanner, at least one month post-scanning each participant was tested in a behavioural study, and the behavioural data were related to connectivity estimates. This behavioural test used the stimuli from the fMRI study [minus the acoustic baseline items] with an additional 132 unambiguous filler sentences which had unacceptable continuations. Participants heard, in a female voice, an initial sentence fragment ending with an ambiguous or unambiguous phrase. At the offset of the fragment, a continuation verb, consistent with either the subordinate (least preferred) or dominant (most strongly preferred) interpretation, was presented in a male voice. Participants made a yes/no response to indicate whether the verb was an acceptable or unacceptable continuation of the sentence fragment. Although all continuations (including the subordinate ones) were acceptable, subordinate continuations were incongruent with the preferred interpretation of the ambiguous phrase and participants had to revise their interpretation in order to resolve the temporary incompatibility.

Diffusion Tensor Imaging (DTI) analysis

We assessed the integrity of two white matter tracts which have been implicated in language function – the arcuate fasciculus and the extreme capsule fibre system – in patients and controls by constructing standard space templates for these two tracts in each hemisphere, and obtaining probabilistically-weighted measures of Fractional Anisotropy (FA) and Mean Diffusivity (MD) for each subject from the regions defined by these templates following the method of Hua et al. (2008; see Supplementary materials for details of analysis). We did not have DTI data for one patient and two controls so they were not included in the DTI analysis.

Results

Behavioural post-test

The control group made a large percentage of unacceptable judgements [42.4%] when the continuation was consistent with the subordinate reading, and a small percentage [8.8%] when it was consistent with the dominant reading ($t(14) = 7.0$, p<0.001). This pattern of behaviour (more unacceptable judgements for subordinate conditions) reflects the sensitivity of the healthy control group to the incongruence between the subject's preference (dominant continuation) and encountering the subordinate continuation. The patient group also showed a difference between the two conditions (36.2% for subordinate, 26% for dominant; $t(13) = 2.6$, p = 0.02), but the difference was much smaller than for the controls ($t(27) = 3.8$, p<0.001; mean subordinate-dominant difference controls = 34%, patients = 10%; Tyler et al., 2011). This reduced differentiation between performance in the subordinate and dominant conditions in the patients, which showed considerable variability within the patient group, reflects individual patients' problems with syntactic processing. Performance on this task correlated significantly with performance on other tests of syntax such as sentence-picture matching (Tyler et al., 2011), with decreasing number of syntactic errors correlating with increased percent unacceptable judgements between subordinate and dominant sentences (Spearman's r = −0.65, p = 0.013). This result shows the consistency of the syntactic processing deficit across different tests of syntax. We used the difference in percent of unacceptable judgements between subordinate and dominant sentences as our measure of syntactic sensitivity (Tyler et al., 2011) in subsequent correlations with connectivity measures.

Effective connectivity results

We first measured effective connectivity between the LIFG and LpMTG and the rest of the brain for the control group using the two seed ROIs from the subordinate-dominant contrast in the controls (Tyler et al., 2011). When seeding the effective connectivity analysis from the LIFG we found a significant effect with the LpMTG (MNI: −66 −30 0; see Table 1 and Fig. 2A), stronger for subordinate compared to dominant sentences. Connectivity between LIFG and LpMTG was present only when the seed ROI was in the LIFG (BA47/45); connectivity seeded from the LpMTG did not show a positive effect with the LIFG or any other brain region. The positive PPI effect between the LIFG and the LpMTG can potentially be interpreted
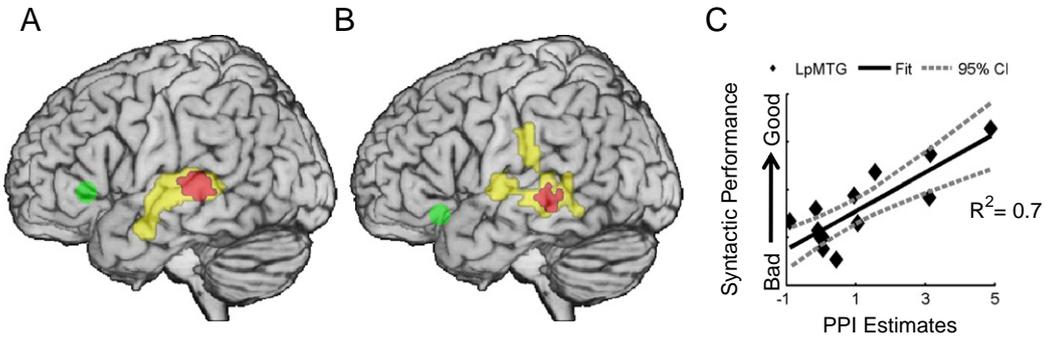
as either an increase in the influence of the seed region (LIFG) on the target region (LpMTG) or a decrease from the target to the seed region. The direction of the influence cannot be disambiguated using PPI alone. However, based on our a priori hypothesis that left fronto-temporal effective connectivity increases as a function of syntactic processing, together with evidence from a DCM analysis showing an increase in left fronto-temporal connectivity driven by the LIFG as a function of increased syntactic processing (den Ouden et al., 2010), we can also infer that in our case LH fronto-temporal effective connectivity increases as a function of syntactic processing driven by the LIFG (BA47/45).

There were no negative PPI effects when the seed was in the LIFG. However, coupling decreased between the LpMTG and bilateral anterior cingulate/medial prefrontal cortex (cluster peaks were in LaCG and RmedPFC; MNI: −9 39 −6 and 3 48 6 respectively; see Table 1), bilateral precuneus (Pre; MNI: 6 −66 33; see Table 1) and the LH middle occipital gyrus (LMOG; MNI: −33 −96 0; see Table 1), most plausibly reflecting task-related deactivations, when comparing high- and low-demand conditions, as in the case of the subordinate vs. dominant comparison (Fox et al., 2005; Shulman et al., 1997).

To determine whether LH fronto-temporal connectivity is essential for intact syntactic processing – our main question of interest – we correlated connectivity strength with syntactic processing ability in the patients. If LH fronto-temporal connectivity is essential for successful syntactic processing, then reduced connectivity between these regions should correlate with impaired syntactic performance. Our measure of syntactic performance was the difference in acceptability judgements to the subordinate and dominant sentences, with a smaller difference indicating poorer sensitivity to syntax (Tyler et al., 2011). We regressed this measure with our measure of effective connectivity (whole-brain PPI contrast estimates) and found that syntactic performance significantly predicted LH fronto-temporal connectivity. More specifically, when using the LIFG (BA47/45) seed region, reduced coupling with a region primarily centred on the LpMTG (MNI: −60 −30 0; see Table 1) and extending into the STG and rolandic operculum correlated with poorer syntactic processing ability (see Figs. 2B and C). As in the case of the controls, this effect was specific for the LIFG and there were no significant correlations between behaviour and connectivity when using the LpMTG as a seed region, either positive or negative.

Structural connectivity results

Turning to structural connectivity, we measured the degree of damage to the arcuate fasciculus (AF) and extreme capsule fibre system (ECFS) using probabilistically-weighted spatial averages (see Supplementary materials) of two standard tensor-derived quantities: Mean Diffusivity (MD), which quantifies the average amount of water diffusion within a voxel irrespective of direction, and Fractional Anisotropy (FA), which represents the degree of directionality (anisotropy) of water diffusion within a voxel (Le Bihan et al., 2001). These two metrics are therefore expected to show approximately inverse relations with damage in tissues such as axonal fibre bundles that exhibit high orientational coherence at the microstructural level — with decreased FA and increased MD relative to normal levels both indicating increased white matter damage. Because of the large difference in between-group variance for comparisons with the LH tracts (Levene's test for equality of variance was significant at p<0.001 for all LH between-group comparisons), we performed separate repeated measures ANOVAs for the control and patient groups with factors of hemisphere (left/right) and tract (AF/ECFS). At the group level, the patients showed increased damage in both LH tracts (Fig. 3) with significant main effects of hemisphere for both FA ($F(1,12) = 27.28$, p<0.001) and MD ($F(1,12) = 14.66$, p = 0.002). Paired t-tests confirmed decreased FA and increased MD in patients' LH vs. RH in both the AF (FA: $t(12) = −5.69$, p<0.001; MD: $t(12) = 3.58$,

Table 1
Effective connectivity results.

Seed * contrast	Cluster		Peak voxel			
Region	P FWE-corr	Extent	x	y	z	Z-score
Controls						
LIFG (BA 47/45) * subordinate>dominant						
LpMTG (BA 21)	0.011	339	−66	−30	0	4.30
LSTG (BA 22)			−60	−6	−6	3.84
LpMTG (BA 21) * dominant>subordinate						
RmedPFC (BA 10)	0.000	708	27	48	0	3.71
RaCG (BA 10)			3	48	6	3.68
LMOG (BA 18)	0.036	252	−33	−96	0	3.29
RPre	0.043	242	6	−66	33	3.55
Patients: regression with performance						
LIFG (BA 47/45) * subordinate>dominant						
LpMTG (BA 21)	0.035	372	−60	−30	0	3.78
LROp (BA 13)			−42	−18	15	3.45

Cluster extent given in number of voxels. Voxel-level threshold: p<0.01 uncorrected. BA = Brodmann area. IFG = inferior frontal gyrus. pMTG = posterior middle temporal gyrus. STG = superior temporal gyrus. ROp = rolandic operculum. aCG = anterior cingulate gyrus. medPFC = medial prefrontal cortex. MOG = middle occipital gyrus. Pre = precuneus.

Fig. 2. The PPI results for (A) the controls and (B) the patients for the subordinate vs. dominant contrast, using the LIFG seed region (green circle). The results are shown at two thresholds: yellow indicates results at voxel-level p<0.01, cluster FWE-corrected p<0.05; red shows results at a more conservative threshold of voxel-level .001. (C) shows the regression line (with 95% confidence interval; CI) between performance (difference in % unacceptable judgments for subordinate − dominant) and contrast estimates from the LpMTG cluster shown in (B) at p<0.01 voxel-level threshold. Contrast estimates were extracted from the regression with performance in the patient group (ROI seed in the LIFG) and summarised across all voxels of the cluster by the first eigenvalue.
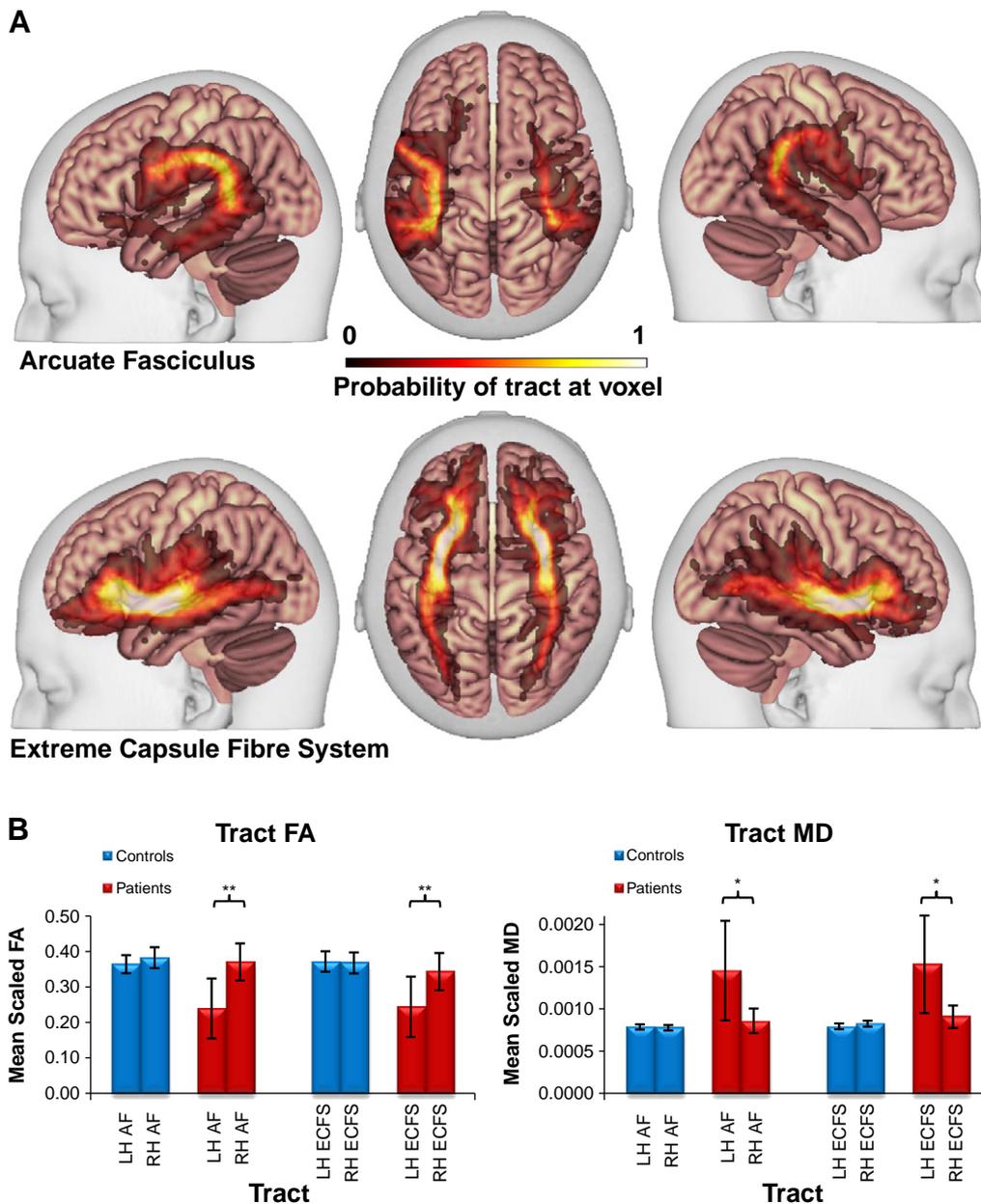
Fig. 3. Differences in white matter integrity in patients and controls. (A) Tract probability maps for arcuate fasciculus and extreme capsule fibre system. (B) Mean (SD) tract Fractional Anisotropy (FA) and Mean Diffusivity (MD) values. Patients show decreased FA and increased MD in LH vs. RH for both AF and ECFS (**p<0.001, *p<0.01).

p = 0.004) and ECFS (FA: $t(12) = -4.34$, p = 0.001; MD: $t(12) = 3.92$, p = 0.002). The control group in contrast did not show any hemispheric differences for either FA or MD measures (FA: $F(1,12) = 1.89$, p = 0.195; MD: $F(1,12) = 2.86$, p = 0.117). To further examine the hemispheric differences in tract damage between the two groups we also performed separate two-sample *t*-tests for the between-group comparisons, where p-values were adjusted for heterogeneity of variance and corrected for multiple comparisons (Bonferroni correction for 4 tests). The results confirmed that there was a significant difference between the two groups for both LH white matter tracts, but not the RH tracts. The patient group FA values for the LAF (mean (SD) = 0.24(0.08)) and LECFS (mean (SD) = 0.24 (0.09)) were significantly lower (LAF $t(14.2) = -5.1$, p < 0.001; LECFS $t(14.7) = -5.1$, p < 0.001) than those of the controls (LAF mean (SD) = 0.36 (0.03), LECFS mean (SD) = 0.37 (0.03)) and vice versa for the MD estimates for the LAF (patients' mean (SD) = 0.0014 (0.0006); controls' mean (SD) = 0.0008 (0.00003); $t(12.1) =$ 3.9, p = 0.008) and LECFS (patients' mean (SD) = 0.0015 (0.0006); controls' mean (SD) = 0.0008 (0.00003); $t(12.1) = 4.5$, p = 0.003). For the RH comparisons there was no difference between the two groups in both FA and MD comparisons (p > 0.3 for all RAF and RECFS comparisons). These results show that at the group level, left hemisphere fronto-temporal structural connectivity is damaged in the patients, although there is large degree of inter-subject variability in the damage as can be seen in Fig. 3B.

Because there was considerable variability within the patient group in terms of syntactic processing ability, we were able to correlate MD and FA values with syntactic performance and we found that impaired syntactic processing ability correlated with increasing MD and decreasing FA in both LECFS (MD: Spearman's $r = -0.69$, p = 0.005 1-tailed; FA Spearman's $r = 0.60$, p = 0.015 1-tailed) and LAF (MD: Spearman's $r = -0.58$, p = 0.01 1-tailed; FA Spearman's $r = 0.58$, p = 0.01 1-tailed). This was not the case for the correlations with RH tracts (for all Spearman's correlations p > 0.2 1-tailed). These results highlight the importance of intact LH fronto-temporal fibre bundles for preserved syntactic processing.

Correlating MD and FA values with PPI estimates extracted from the LpMTG cluster shown in Fig. 2B in the patient group further highlights the role of these two LH fibre tracts as pathways of communication between the LIFG and LpMTG during syntactic processing. Decreased LIFG–LpMTG effective connectivity for the subordinate vs. dominant sentences shows a marginal correlation with increased MD and reduced FA for both the LECFS (MD: Spearman's $r = -0.47$, p = 0.05 1-tailed; FA Spearman's $r = 0.42$, p = 0.07 1-tailed) and the LAF (MD: Spearman's $r = -0.42$, p = 0.07 1-tailed; FA Spearman's $r = 0.40$, p = 0.09 1-tailed) and is suggestive of the relationship between effective and structural connectivity within the LH. This was not the case for the correlations with RH tracts (for all Spearman's correlations p > 0.2 1-tailed).

Discussion

In previous studies, we and others have shown that the left inferior frontal cortex and middle temporal gyrus are co-activated during syntactic processing (Caplan et al., 2008; Dapretto and Bookheimer, 1999; Keller et al., 2001; Rodd et al., 2010; Tyler and Marslen-Wilson, 2008; Tyler et al., 2010, 2011). Here we test the hypothesis that it is the effective connectivity between these regions that is essential for successful syntactic processing. We first obtained baseline measures of effective connectivity from a group of healthy controls. We then calculated measures of effective connectivity in patients with acquired LH brain damage and variability in both lesion location and syntactic processing ability and correlated connectivity estimates with measures of syntactic processing performance. This kind of approach, with the focus on brain-damaged patients, allows much stronger inferences to be drawn about the essential contribution of fronto-temporal connectivity to performance (Chatterjee, 2005). Our

measure of syntactic performance involved syntactic ambiguity, in which we manipulated the preference strength for one syntactic interpretation over the other. The behavioural performance of healthy subjects showed that they initially based their interpretation of a syntactically ambiguous phrase on its dominant reading, which needed to be revised when the continuation was consistent with the subordinate reading. The patients, in contrast, showed considerable variability in their sensitivity to preference strength, reflecting their difficulties with syntactic analysis.

We calculated the effect of the interaction between the activity of two seed ROIs (LIFG and LpMTG) and the difference between subordinate and dominant sentence disambiguation across the whole brain (PPI), and then correlated effective connectivity with variability in syntactic processing ability in the patient group. This variability in syntactic ability correlated significantly with estimates of effective connectivity between the LIFG and LpMTG, indicating that good syntactic performance was associated with increased fronto-temporal connectivity, driven by the LIFG. Additional analyses, measuring the integrity of the two anatomical pathways – the arcuate fasciculus and extreme capsule fibre system – which directly connect inferior frontal and middle temporal regions, showed that FA and MD measurements from both tracts in the LH also correlated with syntactic processing ability. Finally, increasing FA and decreasing MD values also correlated with increasing fronto-temporal connectivity. Taken together, these findings highlight the role of LH fronto-temporal connectivity, both structural and effective, during syntactic processing and reveal that structural and effective connectivity within the LH is essential for preserved syntactic processing and disruption of LH connectivity will lead to syntactic processing deficits. Disruption to LH fronto-temporal effective connectivity can occur as a result of both grey matter damage in the LIFG and LpMTG and white matter damage in tracts connecting the LIFG and LpMTG. We have previously shown the structural damage to the LIFG and LpMTG leads to syntactic processing impairments (Tyler et al., 2011). In this paper we extend these results to show that damage to the white matter tracts that connect the LIFG and LpMTG also leads to syntactic processing impairments. More importantly we show that what underlies syntactic processing deficits is the compromise of left hemisphere fronto-temporal effective connectivity, which is essential for preserved syntactic processing and anatomically supported by the LAF and LECFS.

In contrast to the finding reported here of a significant relationship between syntactic performance and effective connectivity, in a previous analysis we found that performance did not correlate with neural activity *per se* for the patients in the subordinate-dominant contrast (Tyler et al., 2011). This suggests that it is indeed the temporal coupling between LIFG and LpMTG that is critical in syntactic analysis and not merely the co-activation of these regions, raising the key issue of what function this coupling serves in syntactic processing. To address this issue we need to consider the cognitive processes involved in constructing syntactic representations from speech inputs. Many current models of language processing are lexicalist in nature, taking as their starting point the claim that as each word is heard its syntactic and semantic properties are activated in parallel. The contextually relevant aspects of these lexical representations are integrated into the developing sentential and discourse representation such that words are combined into structured sequences through processes of syntactic combination (Marslen-Wilson and Tyler, 1975, 1980; Snijders et al., 2009, 2010; Tyler and Marslen-Wilson, 1977, 2008).

In the present study, processes of syntactic combination are highlighted in the contrast between the subordinate and dominant ambiguity conditions. Listeners base their initial interpretation of the ambiguous phrase on its dominant reading, and when this turns out to be inconsistent with the upcoming word (in the subordinate condition), they must revise their initial interpretation in order to integrate the new information into a coherent sentential representation. We assume that

the temporal coupling between LIFG and LpMTG, instantiated by the white matter tracts which directly connect them, provides the neural mechanism for these processes of activation and integration. We also assume that this coupling is an intrinsic aspect of spoken language comprehension, and that syntactic ambiguity which involves revision of initial syntactic analyses merely highlights this coupling due to its enhanced effects.

A putative mechanism within which this coupling may be instantiated is the basic neurobiological property of cortico–cortico connections between distant cortical sites (Schüz et al., 2006). These bidirectional connections allow for the possibility that complex cognitive functions – such as language processing – involve the recurrent flow of activity across distant cortical regions, re-entrant activity and top–down modulation. Within this neurobiological context, the temporal dependencies between frontal and temporal regions in the context of syntactic re-analysis may involve re-entrant activity in the LpMTG as a function of top–down signals from the LIFG indicating an incompatibility between the input and existing representation in the subordinate condition. Re-entrant activity in the LpMTG may serve to enhance activity of the less preferred syntactic interpretation of the ambiguity, so enabling the development of an appropriately integrated sentential representation.

Similar results showing effective connectivity between the LIFG and LpMTG in the context of syntactic processing come from a recent study contrasting form-class ambiguous (noun–verb ambiguity) and unambiguous words which occurred in written sentences or in word lists (Snijders et al., 2010). When ambiguous words occurred in sentences, but not in word lists, there was significant coupling, as measured by PPI, between a widespread network of regions. This included connectivity between L frontal regions (BA 44/6/9) and LpMTG, and between LpMTG and a variety of bilateral frontal and temporal regions. The RH connectivity is somewhat puzzling here. While it is widely acknowledged that LH regions are involved in syntactic processing, the contribution of the RH is more controversial. We have argued that the RIFG cannot perform syntactic computations, and have shown that even when the RIFG and the RMTG are co-activated in syntactic processing, the activity in these regions is not correlated with variations in syntactic performance. This stands in contrast to the LIFG and the LpMTG which we argue form the essential core of syntactic processing in spoken language (Tyler and Marslen-Wilson, 2008; Tyler et al., 2010, 2011). Within this framework, the likely function of activity in the RH is to support, rather than replace, the activity in the LH during syntactic processing. This raises the possibility that at least some of the RH connectivity observed in the Snijders et al. (2010) study may reflect task-related processes rather than the core language processes. This possibility is hard to evaluate, given that the study did not test the relationship between syntactic performance and connectivity measures. In the current study we used passive listening in order to avoid potential task-related activations in the LIFG, which may be difficult to differentiate from language-related activity (Wright et al., 2011). This is in keeping with other studies (Crinion and Price, 2005; Crinion et al., 2003, 2006; Warren et al., 2009) that have also used passive listening. Despite the fact that there was no explicit response made to the sentences heard in the scanner, the linguistic manipulations generated similar patterns of primarily left fronto-temporal activity for syntactic processing as we and others have reported in previous studies (Caplan et al., 2008; Snijders et al., 2009, 2010; Tyler et al., 2010). This may reflect the automatic and obligatory nature of spoken language comprehension (Marslen-Wilson et al., 1981; Marslen-Wilson and Tyler, 1975).

The findings reported here illustrate the critical role that data from brain damaged patients can play in clarifying the neural basis of cognitive functions. Variability in both the patients' cognitive performance and in their lesion locations provides important constraints on the inferences we can draw (Chatterjee, 2005). If we had relied solely on the data from healthy participants, or on a group of brain-damaged patients who had a restricted set of lesions, the lack

of performance variability would have reduced the probability of seeing any systematic relationship between measures of connectivity and measures of performance.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.06.036.

References

Ashburner, J., Friston, K.J., 2005. Unified segmentation. NeuroImage 26 (3), 839–851.
Burock, M.A., Buckner, R.L., Woldorff, M.G., Rosen, B.R., Dale, A.M., 1998. Randomized event-related experimental designs allow for extremely rapid presentation rates using functional MRI. NeuroReport 9 (16).
Caplan, D., Hildebrandt, N., Makris, N., 1996. Location of lesions in stroke patients with deficits in syntactic processing in sentence comprehension. Brain 119 (3), 933–949.
Caplan, D., Alpert, N., Waters, G., 1999. PET studies of syntactic processing with auditory sentence presentation. NeuroImage 9 (3), 343–351.
Caplan, D., Alpert, N., Waters, G., Olivieri, A., 2000. Activation of Broca's area by syntactic processing under conditions of concurrent articulation. Hum. Brain Mapp. 9 (2), 65–71.
Caplan, D., Stanczak, L., Waters, G., 2008. Syntactic and thematic constraint effects on blood oxygenation level dependent signal correlates of comprehension of relative clauses. J. Cogn. Neurosci. 20 (4), 643–656.
Catani, M., Jones, D.K., ffytche, D.H., 2005. Perisylvian language networks of the human brain. Ann. Neurol. 57 (1), 8–16.
Chatterjee, A., 2005. A madness to the methods in cognitive neuroscience? J. Cogn. Neurosci. 17 (6), 847–849.
Crinion, J., Price, C.J., 2005. Right anterior superior temporal activation predicts auditory sentence comprehension following aphasic stroke. Brain 128 (12), 2858–2871.
Crinion, J.T., Lambon-Ralph, M.A., Warburton, E.A., Howard, D., Wise, R.J.S., 2003. Temporal lobe regions engaged during normal speech comprehension. Brain 126 (5), 1193–1201.
Crinion, J.T., Warburton, E.A., Lambon-Ralph, M.A., Howard, D., Wise, R.J.S., 2006. Listening to narrative speech after aphasic stroke: the role of the left anterior temporal lobe. Cereb. Cortex 16 (8), 1116–1125.
Crinion, J., Ashburner, J., Leff, A., Brett, M., Price, C., Friston, K., 2007. Spatial normalization of lesioned brains: performance evaluation and impact on fMRI analyses. NeuroImage 37 (3), 866–875.
Dapretto, M., Bookheimer, S.Y., 1999. Form and content: dissociating syntax and semantics in sentence comprehension. Neuron 24 (2), 427–432.
den Ouden, D.-B., Saur, D., Schelter, B., Luki, S., Wali, E., Thompson, C.K., 2010. Network modulation during complex syntactic processing. Presented at the 2nd Neurobiology of Language Conference, San Diego, CA, USA.
Dronkers, N.F., Wilkins, D.P., Van Valin, R.D., Redfern, B.B., Jaeger, J.J., 2004. Lesion analysis of the brain areas involved in language comprehension. Cognition 92 (1–2), 145–177.
Fox, M.D., Snyder, A.Z., Vincent, J.L., Corbetta, M., Van Essen, D.C., Raichle, M.E., 2005. The human brain is intrinsically organized into dynamic, anticorrelated functional networks. Proc. Natl. Acad. Sci. U. S. A. 102 (27), 9673–9678.
Friederici, A.D., 2009. Pathways to language: fiber tracts in the human brain. Trends Cogn. Sci. 13 (4), 175–181.
Friston, K.J., Holmes, A.P., Worsley, K.J., Poline, J.-P., Frith, C.D., Frackowiak, R.S.J., 1994. Statistical parametric maps in functional imaging: a general linear approach. Hum. Brain Mapp. 2 (4), 189–210.
Friston, K.J., Buechel, C., Fink, G.R., Morris, J., Rolls, E., Dolan, R.J., 1997. Psychophysiological and modulatory interactions in neuroimaging. NeuroImage 6 (3), 218–229.
Glasser, M.F., Rilling, J.K., 2008. DTI tractography of the human brain's language pathways. Cereb. Cortex 18 (11), 2471–2482.
Griffiths, J.D., Stamatakis, E.A., Tyler, L.K., 2009. Damage to dorsal and ventral frontotemporal white matter pathways impairs syntactic aspects of language comprehension: a DTI tractography study. NeuroImage 47 (S143).
Hua, K., Zhang, J., Wakana, S., Jiang, H., Li, X., Reich, D.S., Calabresi, P.A., et al., 2008. Tract probability maps in stereotaxic spaces: analyses of white matter anatomy and tract-specific quantification. NeuroImage 39 (1), 336–347.
Kaan, E., Swaab, T.Y., 2002. The brain circuitry of syntactic comprehension. Trends Cogn. Sci. 6 (8), 350–356.

Keller, T.A., Carpenter, P.A., Just, M.A., 2001. The neural bases of sentence comprehension: a fMRI examination of syntactic and lexical processing. Cereb. Cortex 11 (3), 223–237.

Le Bihan, D., Mangin, J.-F., Poupon, C., Clark, C.A., Pappata, S., Molko, N., Chabriat, H., 2001. Diffusion tensor imaging: concepts and applications. J. Magn. Reson. Imaging 13 (4), 534–546.

Ludlow, C.L., Rosenberg, J., Fair, C., Buck, D., Schesselman, S., Salazar, A., 1986. Braiin lesions associated with nonfluent aphasia fifteen years following penetrating head injury. Brain 109 (1), 55–80.

MacDonald, M.C., Pearlmutter, N.J., Seidenberg, M.S., 1994. The lexical nature of syntactic ambiguity resolution. Psychol. Rev. 101 (4), 676–703.

Makris, N., Pandya, D., 2009. The extreme capsule in humans and rethinking of the language circuitry. Brain Struct. Funct. 213 (3), 343–358.

Maldjian, J.A., Laurienti, P.J., Kraft, R.A., Burdette, J.H., 2003. An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage 19 (3), 1233–1239.

Marslen-Wilson, W.D., Tyler, L.K., 1975. Processing structure of sentence perception. Nature 257 (5529), 784–786.

Marslen-Wilson, W., Tyler, L.K., 1980. The temporal structure of spoken language understanding. Cognition 8 (1), 1–71.

Marslen-Wilson, W.D., Tyler, L.K., Page, R.B.L., 1981. Central processes in speech understanding [and discussion]. Philos. Trans. R. Soc. Lond. B Biol. Sci. 295 (1077), 317–332.

McRae, K., Spivey-Knowlton, M.J., Tanenhaus, M.K., 1998. Modeling the influence of thematic fit (and other constraints) in on-line sentence comprehension. J. Mem. Lang. 38 (3), 283–312.

Ostrin, R.K., Tyler, L.K., 1995. Dissociations of lexical function: semantics, syntax, and morphology. Cogn. Neuropsychol. 12 (4), 345–389.

Passamonti, L., Rowe, J.B., Ewbank, M., Hampshire, A., Keane, J., Calder, A.J., 2008. Connectivity from the ventral anterior cingulate to the amygdala is modulated by appetitive motivation in response to facial signals of aggression. NeuroImage 43 (3), 562–570.

Price, C.J., Crinion, J., Friston, K.J., 2006. Design and analysis of fMRI studies with neurologically impaired patients. J. Magn. Reson. Imaging 23 (6), 816–826.

Rodd, J.M., Longe, O.A., Randall, B., Tyler, L.K., 2010. The functional organisation of the fronto-temporal language system: evidence from syntactic and semantic ambiguity. Neuropsychologia 48 (5), 1324–1335.

Saur, D., Kreher, B.W., Schnell, S., Kümmerer, D., Kellmeyer, P., Vry, M.-S., Umarova, R., et al., 2008. Ventral and dorsal pathways for language. Proc. Natl. Acad. Sci. 105 (46), 18035–18040.

Schüz, A., Chaimow, D., Liewald, D., Dortenman, M., 2006. Quantitative aspects of corticocortical connections: a tracer study in the mouse. Cereb. Cortex 16 (10), 1474–1486.

Shulman, G.L., Fiez, J.A., Corbetta, M., Buckner, R.L., Miezin, F.M., Raichle, M.E., Petersen, S.E., 1997. Common blood flow changes across visual tasks: II. decreases in cerebral cortex. J. Cogn. Neurosci. 9 (5), 648–663.

Snijders, T.M., Vosse, T., Kempen, G., Van Berkum, J.J.A., Petersson, K.M., Hagoort, P., 2009. Retrieval and unification of syntactic structure in sentence comprehension: an fMRI study using word-category ambiguity. Cereb. Cortex 19 (7), 1493–1503.

Snijders, T.M., Petersson, K.M., Hagoort, P., 2010. Effective connectivity of cortical and subcortical regions during unification of sentence structure. NeuroImage 52 (4), 1633–1644.

Stamatakis, E.A., Tyler, L.K., 2005. Identifying lesions on structural brain images—validation of the method and application to neuropsychological patients. Brain Lang. 94 (2), 167–177.

Stephan, K.E., 2004. On the role of general system theory for functional neuroimaging. J. Anat. 205 (6), 443–470.

Tyler, L.K., Marslen-Wilson, W.D., 1977. The on-line effects of semantic context on syntactic processing. J. Verbal Learn. Verbal Behav. 16 (6), 683–692.

Tyler, L.K., Marslen-Wilson, W., 2008. Fronto-temporal brain systems supporting spoken language comprehension. Philos. Trans. R. Soc. B Biol. Sci. 363 (1493), 1037–1054.

Tyler, L.K., Marslen-Wilson, W.D., Stamatakis, E.A., 2005. Differentiating lexical form, meaning, and structure in the neural language system. Proc. Natl. Acad. Sci. U. S. A. 102 (23), 8375–8380.

Tyler, L.K., Wright, P., Randall, B., Marslen-Wilson, W.D., Stamatakis, E.A., 2010. Reorganization of syntactic processing following left-hemisphere brain damage: does right-hemisphere activity preserve function? Brain 133 (11), 3396–3408.

Tyler, L.K., Marslen-Wilson, W.D., Randall, B., Wright, P., Devereux, B.J., Zhuang, J., Papoutsi, M., et al., 2011. Left inferior frontal cortex and syntax: function, structure and behaviour in patients with left hemisphere damage. Brain 134 (2), 415–431.

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., et al., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. NeuroImage 15 (1), 273–289.

Uppenkamp, S., Johnsrude, I.S., Norris, D., Marslen-Wilson, W., Patterson, R.D., 2006. Locating the initial stages of speech-sound processing in human temporal cortex. NeuroImage 31 (3), 1284–1296.

Warren, J.E., Crinion, J.T., Lambon Ralph, M.A., Wise, R.J.S., 2009. Anterior temporal lobe connectivity correlates with functional outcome after aphasic stroke. Brain 132 (12), 3428–3442.

Wright, P., Randall, B., Marslen-Wilson, W.D., Tyler, L.K., 2011. Dissociating linguistic and task-related activity in the left inferior frontal gyrus. J. Cogn. Neurosci. 23 (2), 404–413.