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Cingulate control of fronto-temporal integration reflects linguistic demands: A three-way interaction in functional connectivity

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In a recent fMRI language comprehension study, we asked participants to listen to word-pairs and to make same/different judgments for regularly and irregularly inflected word forms [Tyler, L.K., Stamatakis, E.A., Post, B., Randall, B., Marslen-Wilson, W.D., in press]. We found that a fronto-temporal network, including the anterior cingulate cortex (ACC), left inferior frontal gyrus (LIFG), bilateral superior temporal gyrus (STG) and middle temporal gyrus (MTG), is preferentially activated for regularly inflected words. We report a complementary re-analysis of the data seeking to understand the behavior of this network in terms of inter-regional covariances, which are taken as an index of functional connectivity. We identified regions in which activity was predicted by ACC and LIFG activity, and critically, by the interaction between these two regions. Furthermore, we determined the extent to which these inter-regional correlations were influenced differentially by the experimental context (i.e. regularly or irregularly inflected words). We found that functional connectivity between LIFG and left MTG is positively modulated by activity in the ACC and that this effect is significantly greater for regulars than irregulars. These findings suggest a monitoring role for the ACC which, in the context of processing regular inflected words, is associated with greater engagement of an integrated fronto-temporal language system.

Keywords: Functional connectivity; Language network; fMRI

Introduction

The distinction between regular and irregular inflected words is a major testing ground for theories of how language is represented and processed in mind and brain. These theories argue, on the one hand, that all of language can be processed within a single unified system (Joanisse and Seidenberg, 1999; McClelland and Patterson, 2002), and on the other, that different mechanisms are necessary for dealing with different aspects of linguistic function (Marslen-Wilson and Tyler, 1997, 1998; Tyler et al., 2002a,b). Regular and irregular inflected words have been central in this debate because of the clarity of the contrast they provide between a highly rule-like process—the formation of the regular past tense by adding the affix /-d/ to the verb stem [as in *jump–jumped*; *sigh–sighed*]—and the unpredictable and idiosyncratic processes of irregular past tense formation [as in *think–thought*; *make–made*], applying to a small minority of English verbs, where each case has to be learned and represented separately. This is frequently characterized as a contrast between the domain of words (the lexicon) and the domain of rules (the grammar) (Pinker, 1999). The question is whether processes of regular and irregular inflection can be captured within a single system or whether different mechanisms are required to deal with each type.

In recent years, because behavioral data alone have proved to be inconclusive, attention has turned to neuropsychological and neuroimaging studies in the belief that relating brain to behavior will contribute to a differentiation between these different accounts. Within this context, we have consistently shown that behavioral deficits for regular and irregular inflected forms are associated with damage to different parts of the fronto-temporal language system. Impairments in the processing of regular inflected forms are associated with damage to frontal regions (Tyler et al., 2002a), while impairments for irregular inflected forms are associated with damage to more temporal regions (Ullman et al., 1997; Tyler et al., 2002a). However, given the limitations of the lesion-deficit approach, functional neuroimaging studies with healthy subjects offer an important additional input to this debate. Only a small number of neuroimaging studies comparing regular and irregular inflected forms have been carried out, typically using covert production tasks (e.g., Jaeger et al., 1996; Beretta et al., 2003), and these have been criticized as not appropriately testing single mechanism accounts (Seidenberg and

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Arnoldussen, 2003). More recently, in an fMRI language comprehension study, we contrasted neural activation for regular and irregular inflected forms in English and found that regular inflected past tense forms preferentially activated a fronto-temporal network, including anterior cingulate cortex (ACC), left inferior frontal gyrus (LIFG), bilateral superior temporal gyrus (STG) and bilateral middle temporal gyrus (MTG) (Tyler et al., in press).

This analysis of these data sought to characterize brain responses to these linguistic demands in an alternative and complementary way. Specifically, we wished to evaluate the impact of linguistic processing manipulations in terms of changes in integration (or connectivity) within the pre-specified system rather than in terms of levels of activity in isolated regions. We used an approach that extends earlier proposals of Friston et al. (1997). They presented an analytical approach that lies between a full model-based connectivity analysis and a simple analysis of task-independent correlations between regions (e.g., McIntosh and Gonzalez-Lima, 1993; Horwitz et al., 1992; 1995; Friston et al., 1993; McIntosh et al., 1999; Bullmore et al., 2000; Bokde et al., 2001). In their earlier formulation, Friston and colleagues suggested that the approach could be used to identify how the covariance between any two regions might be modulated by a psychological variable or alternatively by the level of activity in a third region. The former was referred to as a psycho-physiological interaction, the latter as a physio-physiological interaction. In the current approach, we extend this to include both the psychological variable and activity in a third region. Thus, in the terminology used previously, we identified a psycho-physio-physiological interaction.

Our analysis specifically attempted to determine how a fronto-temporal relationship (expressed as a covariance or as functional connectivity) is modulated by levels of anterior cingulate activity. In this respect, we used a similar model to that explored previously in the setting of a memory task (Fletcher et al., 1999). We then determined whether this cingulate modulation of fronto-temporal integration was sensitive to processing demands through the linguistic manipulation. That is, our aim was to test for a three-way interaction in inter-regional correlations (a psycho-physio-physiological interaction, or PPPI), thereby extending the psycho-physiological and physio-physiological interaction approaches. Our approach can be conceived as a hierarchy of questions: First, does activity in LIFG predict activity in temporal cortex (i.e. is there fronto-temporal connectivity)? Second, is fronto-temporal connectivity significantly modulated by cingulate activity? Third, does the cingulate modulation of fronto-temporal connectivity differ according to whether the subject is processing regular or irregular past tenses? This approach is analogous to the analysis of any factorially designed experiment which identifies a series of main effects and interactions. The critical difference between this and more common fMRI analyses, however, is that we were not concerned with magnitude of activation in the key regions but rather with covariance between these regions.

Method

The subtractive analysis in our fMRI study (Tyler et al., in press) revealed that a fronto-temporal network, including bilateral ACC, LIFG and bilateral temporal regions including the STG and MTG (Fig. 1), is preferentially activated for regular past tense forms. We suggested that this reflects the additional processing demands posed by regular inflected forms, requiring modulation of temporal lobe lexical access processes by morphological parsing functions supported by the LIFG. The aim of the connectivity analysis is to explore the properties of these hypothesized context-dependent interactions.

Subjects—imaging

Eighteen volunteers participated in the experiment (9 males, 9 females). They were right-handed native speakers of English, with a mean age of 24 years (SD 7 years) and no known hearing deficits. Each volunteer gave informed consent, and they were paid for their participation in the experiment. Volunteers lay in the scanner, wearing headphones over which spoken stimuli were played out. Their right hand rested on a response box which was used to make their response. We used a sparse imaging design to ensure that scanner noise and delivery of the spoken stimuli did not overlap (Hall et al., 1999). Scanning was carried out on a 3 T Bruker Medspec Advance S300 system at the Wolfson Brain Imaging Center, Cambridge, England, using a gradient-echo EPI sequence (TR = 10 s, TE = 27 ms, flip angle 90°, FOV 25 × 25 cm, 21 oblique slices, 4 mm thick (1 mm gap between slices, 128 × 128 in-plane resolution, 86 repetitions, acquisition time of 3 s per image volume) with head coils, 200 kHz bandwidth and spin-echo-guided reconstruction. T1-weighted scans were acquired for anatomical localization.

Materials and design

Subjects heard pairs of spoken stimuli and were instructed to press one response key if the members of each pair were the same and to press an adjacent response key if they were different. In the test conditions, the stimulus pair consisted of spoken words where the first word in the pair was recorded by a male speaker and the second by a female speaker. The baseline consisted of sequences of pink and white noise which were generated from the test items using PRAAT software (Boersma and Weenink, 1996). Pink noise is created from frequencies that are used in speech, while white noise is created from a broader range of frequencies. Since the baseline items were generated from the test stimuli, we ensured that their duration and prosodic envelope were identical across test and baseline conditions. There were equal numbers of same and different pairs in test and baseline conditions. The choice of baseline task and stimuli was intended to present listeners with an auditory discrimination task that made similar demands to the test materials but without triggering activation of speech and language processing areas in the brain. Stimuli were presented during 7 s followed by a 3-s acquisition. Events were pseudo-randomly organized into 3 sessions of 84 events with equal numbers of items from each condition within each session. The order of sessions was varied across the 18 subjects. All items used were monosyllabic words and nonwords matched on syllable structure. These included sets of real word regulars (*stayed–stay*) and irregulars (*taught–teach*), coupled with phonologically matched real word pseudo-regulars (*jade–jay*) and pseudo-irregulars (*port–peach*), as well as matched nonword pairs (*kayed–kay*, *hort–heach*). The connectivity analysis focuses on the real regular

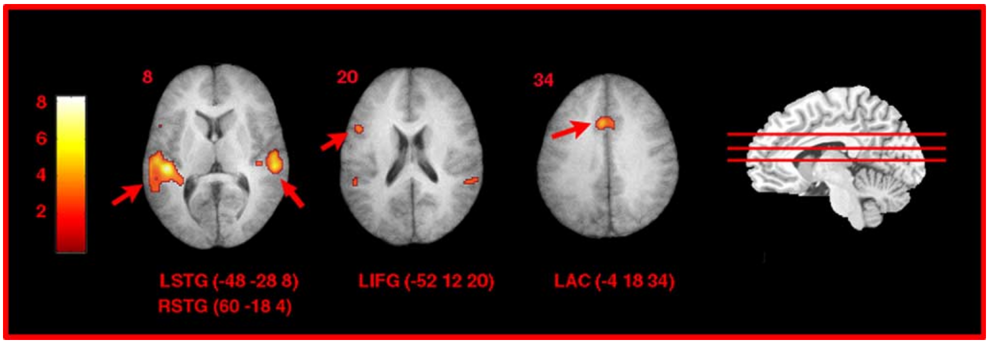

Fig. 1. Findings from the subtractive analysis of this experiment (Tyler et al., in press). Significant clusters (P < 0.05 corrected) are shown for the contrast of real regulars vs. real irregulars.

and irregular inflected words, but we also report results for the pseudo-regulars and -irregulars as a contrast to the real regular/irregular sets.

Analysis procedure

Pre-processing

The analysis of the imaging data was performed using SPM99 (Wellcome Institute of Cognitive Neurology, www.fil.ion.ucl.ac.uk), implemented in Matlab (Mathworks Inc. Sherborn, MA, USA). Pre-processing consisted of image realignment to account for head motion. An un-distortion procedure corrected for EPI distortions due to magnetic field inhomogeneities (Jezzard and Clare, 1999; Cusack et al., 2003). The images were then spatially normalized to a standard Montreal Neurological Institute (MNI) EPI template, using 7 × 8 × 7 nonlinear basis functions, except in areas of low BOLD signal which were masked and excluded from the nonlinear part of the spatial normalization algorithm. We used an isotropic 12 mm full-width half-maximum Gaussian kernel to smooth the images. To enable comparisons to be made with the published subtractive analysis of this study (Tyler et al., in press), we pre-processed the data in an identical manner.

Connectivity analysis

The connectivity analysis is hypothesis-led, requiring the selection of regions of interest, the time series from which are entered into a model as explanatory variables. Activities from all other voxels in the brain are treated as the response variables. Our hypothesis concerned prefrontal cortex (PFC) and anterior cingulate cortex. Subject-specific time series from 2 spherical areas (R = 4vox) centered on the peak activations (LIFG-BA 44 and ACC-BA 32) for the contrast of real regulars vs. real irregulars from the original group analysis (see Figs. 1 and 2) were extracted with the Marsbar toolbox (Brett et al., 2002). In this way, we used the locus of activations from our previous study to constrain the current connectivity analyses. Vectors representing each task condition were convolved with the extracted time series, and these were used as explanatory variables expressing effective connectivity.

There are potential problems associated with identifying psycho-physiological interactions in the context of event-related designs (Gitelman et al., 2003). However, these problems are relevant in the context of fast event-related designs when there is hemodynamic overlap between different event/condition types. The current study used sparse imaging and long SOAs (ca. 10 s) and produced only a single data point for each event, timed to coincide with the peak hemodynamic response for that event. The problems associated with PPI analysis in event-related designs are therefore largely obviated in this case.

The entire analysis implemented the general linear model (Friston et al., 1995). In contrast to the more usual analyses of fMRI data in which the design matrix embodies the experimental design only, our model took into account both design and the levels of activity in the regions of interest: LIFG and ACC. In other words, the predictor variables included experimental condition, ACC activity and LIFG activity, together with the interactions between these variables. A design matrix was created for each subject based upon these three factors: and this was extended to explore all possible two-way interactions (condition-by-LIFG; condition-by-ACC; LIFG-by-ACC) and the three-way interaction (condition-by-LIFG-by-ACC), i.e. the psycho-physio-physiological interaction. Consequently, the design matrix for each subject modeled seven effects of interest (three main effects, three two-way interactions and one three-way interaction). The three-way interaction (i.e. the PPPI or the condition-by-LIFG-by-ACC interaction) was of primary interest given the experimental

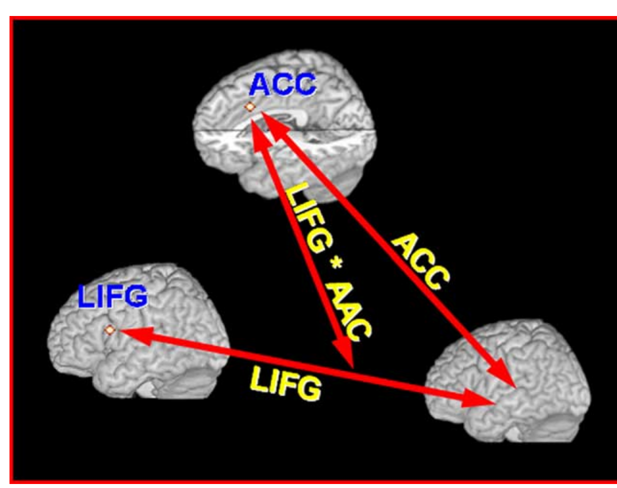

Fig. 2. Schematic representation of the model constructed. Brain activity was expressed in terms of inter-regional correlations of the LIFG and ACC and of modulations of these correlations by other brain regions and by the experimental conditions.

hypothesis. The analysis however required us to include all other effects (main effects of each of the three variables and all two-way interactions) in each subject's model in order to ensure that common effects could be accounted for and that we could identify those effects that were unique to the three-way interaction.

A subject-specific activation map was produced for each of the condition-by-LIFG-by-ACC interactions. Thus, there were four activation maps for each subject:

(i) Real regular inflected words-by-ACC-by-LIFG interaction: in other words, a map identifying regions where LIFG functional connectivity was modulated by ACC in the context of processing real regular words.
(ii) Real irregular inflected words-by-ACC-by-LIFG interaction: as above, but where the ACC modulation of LIFG connectivity occurred in the context of processing real irregular words.
(iii) Pseudo-regular inflected words-by-ACC-by-LIFG.
(iv) Pseudo-irregular inflected words-by-ACC-by-LIFG.

The subject-specific activation maps were taken to a group level analysis, treating inter-subject variability as a random effect. LIFG–ACC interactions that differed according to condition were identified at the group level using paired t tests. Our primary interest lies in the differences in connectivity patterns arising from processing of real regular versus real irregular words. However, given that regular inflected forms and their stems are phonologically more similar than the irregular pairs, it is possible that some differences might reflect variations in task difficulty arising from this similarity. We therefore conducted two subsidiary analyses to evaluate whether our findings could be explained in these terms. First, we conducted a parallel analysis on the pseudo-regularity conditions (i.e. connectivity patterns differing between pseudo-regular and -irregular words) to assess whether this produced similar outcomes. The pseudo-regulars and irregulars share the same phonological relationship as the real regulars and irregulars but not the same linguistic relationship. Second, we investigated the connectivity differences reflecting the interaction between these two factors (real [regular versus irregular] versus pseudo [regular versus irregular]). This enabled us to identify key connectivity patterns differing between regular and irregular words that were not attributable to difficulty differences arising from phonological similarity. This analysis was conducted using a repeated measures ANOVA implemented in SPM.

We were specifically interested in frontal and cingulate connectivity with temporal cortical regions, in particular those overlapping with brain regions identified by the overall subtraction analysis (Tyler et al., in press) comparing words with baseline. We therefore used a masking procedure to constrain our analysis to regions meeting these two criteria. A mask of temporal cortex was created (WFU PickAtlas V1.04; Maldjian et al., 2003), and this was applied to areas identified as significantly activated for speech (Tyler et al., in press). A modified correction for multiple comparisons was applied to the significance of regions showing psycho-physiological interactions on the basis of this constrained analysis. We report clusters that survive the multiple comparison correction at $P < 0.05$. We additionally report MNI coordinates for the peak voxels in each cluster and T scores.

Results

The first set of imaging analyses, comparing real regulars and irregulars, revealed that functional connectivity between LIFG and left MTG and STG (see Fig. 3) is positively modulated by activity in ACC and that this effect is significantly modulated by experimental condition—that is, it is greater for regularly inflected words compared to irregularly inflected words. This constitutes a three-way interaction that can be analyzed in terms of the following integrated effects:

(1) A positive influence of LIFG on temporal activity. We found that activity in the LIFG positively predicts activity in the LMTG and LSTG (peak at MNI −58, −40, −6 [$t = 4.53$]) in the context of regularly inflected words (see Fig. 4). Additionally, activity in the LIFG predicts activity in the LMTG and LSTG (peak at MNI −56, −40, −6 [$t = 4.68$]) in the context of irregularly inflected words (see Fig. 4). Activity in the LIFG does not predict a reduction in activity in the left MTG or STG, so that there is no evidence for a negative relationship between these sites.
(2) A modulatory influence of ACC activity upon this fronto-temporal connectivity. The ACC does not itself predict activity either positively or negatively anywhere in the temporal cortex, but since combined cingulo-frontal activity predicts temporal activity (see Fig. 5), we interpret this as evidence that the ACC exerts a modulatory influence on the fronto-temporal network.
(3) This modulation is condition-specific as reflected in the significant difference between cingulo-fronto-temporal interactions for regularly inflected words compared to irregularly inflected words. The ACC predicts the fronto-temporal interaction in the context of regulars with a peak voxel in the left MTG, MNI −66, −30, 2 [$t = 3.23$] (see Fig. 5). While the ACC also predicts the fronto-temporal interaction in the context of irregulars with peak voxel in the MTG, MNI −54, −24, −12 [$t = 3.30$] (see Fig. 5), the effect is significantly stronger for the regulars. This is shown by the results of paired t tests between the two PPPIs (at the group level) which revealed a significant left MTG cluster with peak at MNI −60, −34, 0 [$t = 3.18$] for the comparison of regulars vs. irregulars, but no significant clusters when irregulars were compared to regulars (see Fig. 3).

Subsidiary analyses to evaluate task difficulty effects

The connectivity analyses on the neuroimaging data for the matched pseudo-regular and pseudo-irregular sets showed no evidence of connectivity differences. This suggests that the findings for the real words are not explicable in terms of the phonological similarity discussed above. It is worth noting, in this connection, that the behavioral data collected while the volunteers were in the scanner did not in any case suggest major differences in difficulty between real regular and irregular sets, with very similar error rates of 5.1% and 4.3%, respectively (Tyler et al., in press).

Critically, the interaction between the four condition specific PPPIs (real regular, real irregular, pseudo-regular, pseudo-irregular) revealed an effect in the MTG (peak at MNI −58, −40, 2 [$t = 2.07$]), thus showing that the real regular vs. real irregular PPPI

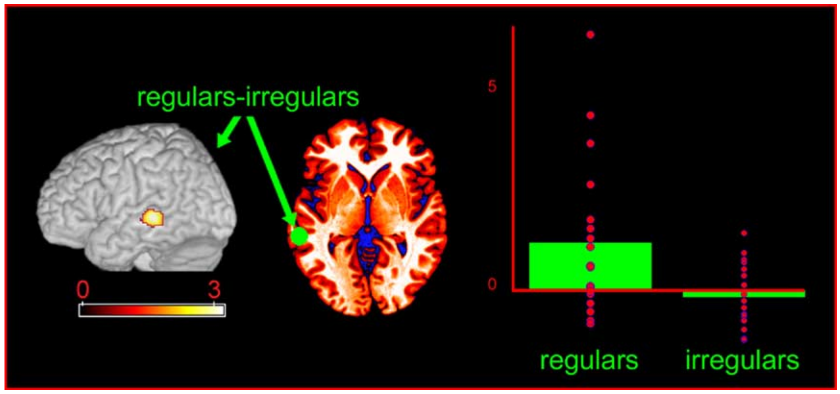

Fig. 3. Connectivity between the cluster shown in the LMTG and the time series extracted from the LIFG is positively predicted by the time series extracted from the LACC, and this effect is significantly modulated by experimental condition (regular > irregular). Axial T1 is shown at Talairach $z = 0$ and left is left. The plot shows effect size for each subject for the two experimental conditions plotted at the peak LMTG voxel (MNI −60, −34, 0). The color bar shows statistical T variation.

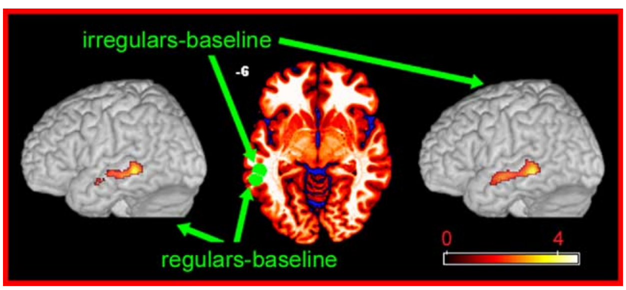

Fig. 4. Activity in the clusters shown in the LMTG for each of the two experimental conditions (regulars–baseline and irregulars–baseline) is positively predicted by the time series extracted from the LIFG. Axial T1 is shown at Talairach $z = -6$ and left is left. The color bar shows statistical T variation.

effect is greater than that of the pseudo-regular vs. pseudo-irregular PPPI.

Discussion

The aim of this analysis was to determine whether connectivity between the cortical regions involved in language processing is modulated as a function of the linguistic variable of morphological regularity. We explored this by assessing task-dependent inter-regional covariation in the left fronto-temporal language network. In this context, we defined our task as the processing of regular and irregular inflected forms and asked whether task-related fluctuations in LIFG and ACC activity predict temporal cortex activity. We also evaluated whether the modulatory effect of the ACC on the fronto-temporal network varies as a function of the different processing demands of regular and irregular inflected words.

Our data support the idea that the presence of the regular affix *-ed* in English past tense forms leads to differential engagement of the cortical fronto-temporal language system. Earlier findings from our subtractive analysis of this data set suggested that the system was engaged to a greater extent by real regular inflected forms (see Fig. 1), a claim that was supported by neuropsychological data showing that, when this region is damaged following stroke, patients have deficits in processing regular inflected words (Tyler et al., 2002a,b). The connectivity analysis contributes to this previous work by offering evidence about the manner in which the constituent components of this fronto-temporal language system interact.

Initially, we asked whether activity in prefrontal areas predicts activity in lateral temporal cortex. The anatomical connectivity between prefrontal and temporal cortices has long been established in the neuroanatomical literature. Structures such as the arcuate fasciculus connect large parts of the frontal association cortices with parietal and temporal association areas (Dejerine, 1895). The uncinate fasciculus also connects frontal (orbital and medial prefrontal) and temporal lobes (entorhinal rostral superior temporal gyrus) (Petrides and Pandya, 1988; Morris et al., 1999). Additionally, findings from functional activation studies suggest a prefrontal

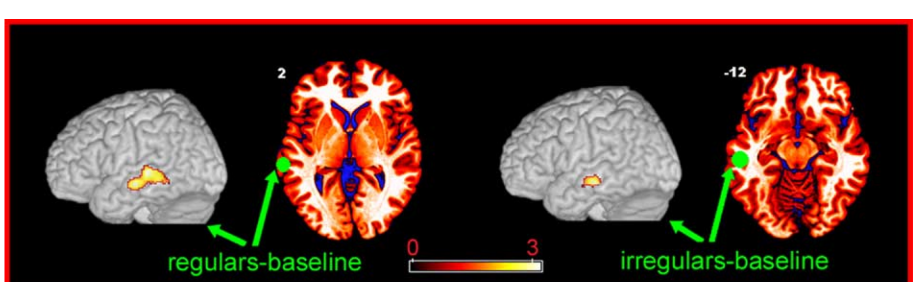

Fig. 5. Connectivity between the clusters shown in the LMTG and the time series extracted from the LIFG is positively predicted by the time series extracted from the LACC for each of the two experimental conditions (regulars–baseline and irregulars–baseline). Axial T1 slices are shown at Talairach $z = 2$ for regulars and Talairach $z = -12$ for irregulars and left is left. The color bar shows statistical T variation.

and temporal interaction in the context of language tasks (Poldrack et al., 1999; Burton et al., 2000; Scott et al., 2000; Binder et al., 2000). In agreement with this evidence, we found that activity in the LIFG predicts activity in the LMTG and LSTG. This may indicate engagement of a ventral language pathway, as proposed in recent reviews by Hickok and Poeppel (2000) and Scott and Johnsrude (2003).

We also determined whether activity in the ACC alone predicts activity in other parts of the brain and found that it did not do so in any region of temporal cortex nor in pre-motor or motor areas, suggesting that its function in this context is independent from the button pressing component of the paradigm. However, activity in the ACC negatively predicted activity in the LIFG. Neuroanatomical findings indicate strong reciprocal connections between the ACC and prefrontal areas (Vogt et al., 1979; Petrides and Pandya, 1988; Goldman-Rakic, 1988). Numerous functional studies have demonstrated co-activation of the ACC and prefrontal areas in the context of response conflict situations (Bush et al., 1998), task-related performance (Osaka et al., 2003; Carter et al., 1998) and monitoring of interactions between different information processing pathways (Braver et al., 2001).

These findings suggest that in our paradigm the ACC has a monitoring role which, in the context of processing real regular inflected words, would reflect greater engagement of an integrated fronto-temporal language system. Morpho-phonological processes, such as the decomposition of regular inflected forms into stems and affixes, may place higher demands on this system, calling on additional resources.

This leads to our key finding of a context-specific influence of the anterior cingulate on the fronto-temporal network, such that the cingulate influence is greater when processing real regular inflected words. While the ACC predicted the fronto-temporal interaction in the context of both real regulars and irregulars, a direct comparison revealed that this interaction was greater when processing real regular inflected words signifying that they engage the fronto-temporal network more strongly than the real irregulars. Although this finding could be alternatively interpreted as a frontal modulation of cingulo-temporal connectivity, evidence from anatomical connectivity (Vogt et al., 1979; Petrides and Pandya, 1988; Goldman-Rakic, 1988; Morris et al., 1999) corroborates our interpretation that the effect we observe here is an ACC modulation of a fronto-temporal network.

These findings for the real past tense forms stand in contrast to the results of the connectivity analyses on the matched pseudo-regular and pseudo-irregular forms. The statistical comparison between the PPPIs describing the anterior cingulate modulation of the frontal and temporal network for these sets did not produce any significant effects nor did the same comparison in the opposite direction (pseudo-irregular vs. pseudo-regulars). Examination of the constituent parts of the interactions revealed that neither the anterior cingulate nor the LIFG plays a significant role in the processing of pseudo-inflected past tense items, although both regions are significantly involved in processing real past tense words, as shown both in the connectivity results presented here and in the earlier subtractive analysis (Tyler et al., in press). Since the pseudo-regulars and -irregulars were phonologically matched to the real items and since the PPPI comparisons for the pseudo-sets and the real sets reveal engagement of different aspects of the speech comprehension network, this allows us to conclude that the significantly greater ACC modulation of the fronto-temporal network shown by the real regulars is driven by their morphological structure as regularly inflected words rather than by purely phonological differences between the different stimulus sets. This conclusion is supported by the interaction between the four condition specific PPPIs (real regular, real irregular, pseudo-regular, pseudo-irregular), showing that in the key MTG region the real regular vs. real irregular PPPI effect is greater than that of the pseudo-regular vs. pseudo-irregular PPPI.

In summary, we have presented a novel approach to the analysis of regular vs. irregular past tense processing. This approach involved the study of the L fronto-temporal language neuronal network as a dynamic integrated system and examined inter-regional modulations of the neuronal systems that constitute parts of the network. Our findings suggest that the anterior cingulate exerts a context-specific modulation on the fronto-temporal language system and that this modulation is significantly elevated when processing regularly inflected forms. As we have argued in more detail elsewhere (Tyler et al., in press), this is likely to reflect a special role of LIFG in processing grammatical morphemes (such as the past tense inflection), and the invocation of these processes when the temporal lobe access system encounters regularly inflected speech inputs, such as the past tense forms studied here.

Acknowledgments

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