A Cortical–Subcortical Syntax Pathway Linking Broca's Area and the Striatum

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Abstract: Combinatorial syntax has been shown to be underpinned by cortical key regions such as Broca's area and temporal cortices, and by subcortical structures such as the striatum. The cortical regions are connected via several cortico-to-cortical tracts impacting syntactic processing (e.g., the arcuate) but it remains unclear whether and how the striatum can be integrated into this cortex-centered syntax network. Here, we used a systematic stepwise approach to investigate the existence and syntactic function of an additional deep Broca-striatum pathway. We first asked 15 healthy controls and 12 patients with frontal/striatal lesions to perform three syntax tests. The results obtained were subjected to voxel-based lesion-symptom mapping (VLSM) to provide an anatomo-functional approximation of the pathway. The significant VLSM clusters were then overlapped with the probability maps of four cortico-cortical language tracts generated for 12 healthy participants (arcuate, extreme capsule fiber system,

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uncinate, aslant), including a probabilistic Broca-striatum tract. Finally, we carried out quantitative analyses of the relationship between the lesion load along the tracts and syntactic processing, by calculating tract-lesion overlap for each patient and analyzing the correlation with syntactic data. Our findings revealed a Broca-striatum tract linking BA45 with the left caudate head and overlapping with VLSM voxel clusters relating to complex syntax. The lesion load values for this tract were correlated with complex syntax scores, whereas no such correlation was observed for the other tracts. These results extend current syntax-network models, by adding a deep "Broca-caudate pathway," and are consistent with functional accounts of frontostriatal circuits. *Hum Brain Mapp 00:000–000, 2015*.

Key words: syntax; Broca; striatum; fiber tracking; pathway

INTRODUCTION

Elucidation of the cerebral bases of syntax, which endows the human species with the unique faculty to infinitely combine words, is one of the key challenges in cognitive neuroscience. All current language models posit the existence of a repertory of word specifications (e.g., words' grammatical category) and a combinatorial component that generatively unifies words according to syntactic constraints. These operations and the corresponding representations are implemented by different regions of the brain that communicate with one another to mediate the flow of information, and constitute a neural network of gray matter structures and white matter connection tracts. Previous research has identified several syntax tracts through the experimental demonstration of their impact on syntactic performance, including the dorsal arcuate route and the ventral extreme capsule fiber system (e.g., Griffiths et al., 2013; Wilson et al., 2011). However, the current view which focuses exclusively on cortical-to-cortical routes appears to be incomplete, because it does not take into account the subcortical gray matter regions known to play a core role in syntactic processing.

It is generally agreed that two cortical regions play a central role in syntax, namely the inferior–posterior frontal cortex (IPFC) including Broca's area (e.g., Dapretto and Bookheimer, 1999; Embick et al., 2000; Friederici et al., 2003; Grodzinsky and Santi, 2008; Just et al., 1996; Pallier et al., 2011) and the superior temporal cortex (e.g., Friederici et al., 2003; Pallier et al., 2011; Snijders et al., 2009). However, various studies have also shown that subcortical gray matter structures, such as the striatum and thalamus, also affect the processing of syntactic operations (e.g., Moro et al., 2001; Wahl et al., 2008). In particular, a major role of the striatum has been demonstrated across different languages, in patient and functional imaging studies, and with different lesion models including Parkinson's disease and Huntington's disease (Friederici et al., 2003; Kemmerer, 1999; McNamara et al., 1996; Moro et al., 2001; Newman et al., 2010; Teichmann et al., 2005, 2008a, 2008b). By contrast, the thalamus has been reported to play a role in syntax in only a few studies (e.g., Wahl et al., 2008), with most authors suggesting that the primary role of this structure concerns lexical-semantic aspects (e.g., Assaf et al., 2006; Crosson, 1985; Kraut et al., 2002; Nadeau and Crosson, 1997).

Fiber tracking has demonstrated that several of the principal gray matter regions involved in syntax are anatomically linked through cortico-to-cortical fiber bundles. In particular, Broca's area (BA44, BA45) and the posterior/mid temporal cortex are connected via fibers of the superior longitudinal/arcuate fasciculus (Catani et al., 2002, 2005) and via the more ventral extreme capsule fiber system (Makris and Pandya, 2009), including the inferior frontooccipital fasciculus (Catani et al., 2002). In addition to these cortico-cortical connections, several investigations have revealed the existence of cortico-subcortical fiber bundles connecting the IPFC to the striatum (Catani et al., 2012; Croxson et al., 2005; Draganski et al., 2008; Ford et al., 2013; Leh et al., 2007; Lehéricy et al., 2004). Several researchers have tried to confirm that these tracts play a genuine function in syntax by assessing the correlation of tract parameters with syntactic performance (e.g., Wilson et al., 2011) and exploring syntactic capacities in patients with and without damage to these tracts (e.g., Griffiths et al., 2013). Such approaches have identified a dorsal and a ventral pathway of syntax linked to fiber contingents of the superior longitudinal fasciculus (Griffiths et al., 2013; Wilson et al., 2011) and the extreme capsule fiber system (Griffiths et al., 2013), respectively. Friederici et al. (2006) also suggested that some aspects of syntax involve a more anterior pathway, passing via the uncinate fasciculus and linking the IPFC to the anterior temporal cortex. However, such brain-syntax studies have focused exclusively on cortico-to-cortical connections and have not taken into account the syntactic role of the subcortical gray matter of the striatum. Conversely, several tracking studies have explored the anatomical connections between Broca's area and the striatum, yet without demonstrating a genuine impact of these connections on syntax (Croxson et al., 2005; Draganski et al., 2008; Ford et al., 2013; Frey et al., 2008; Lehéricy et al., 2004). It is therefore indispensable to expand the current cortex-centered network view by investigating the possible existence of a Broca-striatal pathway impacting on particular aspects of syntax. With this aim in mind, we used a unique combination of behavioral and

multimodal imaging techniques, in both healthy adults and brain-damaged patients, applying a systematic stepwise approach.

We first carried out voxel-based lesion-symptom mapping (VLSM) in patients with left frontal damage to screen for frontal/striatal voxels playing a critical role in three syntax domains shown to be sensitive to damage to Broca's area and the striatum. We hypothesized that this procedure would provide evidence for a continuous gray/white matter voxel cluster linking Broca's area and structures of the left striatum. We then used probabilistic fiber tracking in healthy participants to identify the major cortico-cortical language tracts as well as the putative syntax pathway linking Broca's area and the striatum. Overlapping the tract templates with the VLSM cluster, we expected that only the Broca-striatum tract would demonstrate a substantial overlap with the syntax-related VLSM voxels. Finally, we ran correlation analyses on the lesion loads of the different tracts and the syntactic scores of the patients, predicting that several syntactic aspects would specifically depend on the Broca-striatum tract.

As the outcome of this approach critically depends on the behavioral measures we used tasks tapping into syntactic components reported to involve the striatum and Broca's area, and which were therefore considered likely to depend on a Broca-striatum pathway. In line with studies showing an impact of Broca's area and/or the striatum on the processing of noncanonical sentences (e.g., Ben-Shachar et al., 2003; Kaan and Swaab, 2002; McNamara et al., 1996; Santi and Grodzinski, 2007; Teichmann et al., 2008a, 2008b) we contrasted such phrasal structures (passives, object-relatives) with syntactically less complex sentences having a canonical word order (actives, subject-relatives; Task 1). We furthermore extended the assessment to the domain of verbal morphosyntax, which has also been shown to involve Broca's area and the left striatum (e.g., Laine et al., 1999; Teichmann et al., 2005, 2006, 2008b; Tyler et al., 2005; Vannest et al., 2005). Combinatorial processes of morphosyntax linked to regular inflection ([inflected form] = [verb root] + [suffix]) were contrasted with lexical-based processes of idiosyncratic irregular inflection. Moreover, to ascertain that the assessment of combinatorial processes is independent from the processing modality we tested inflectional operations in both verb production (Task 2) and verb perception (Task 3). We expected that this multi-faceted and contrastive syntax testing would contribute to confirm and specify the syntactic role of the predicted Broca-striatum pathway.

METHODS

Participants

We investigated 12 patients (8 men and 4 women) with lesions at various sites in the left frontal lobe and/or the left striatum. The lesions resulted from the resection of WHO grade II gliomas, performed at least nine months before inclusion in the study. The patients had no previous neurological or psychiatric history other than glioma. Brain surgery was carried out under local anesthesia allowing for the application of a naming task during electrical brain stimulation. This stimulation-guided resection technique (e.g., Duffau et al., 2002, 2005) guaranteed the selection of patients without significant lexical disorders. The application of a picture naming test (DO80; Deloche and Hannequin, 1997) at the time of inclusion in the study confirmed the preservation of naming abilities, ensuring that lexical-related biases in sentence comprehension tasks were minimal. By contrast, syntactic performance in the sentence-picture matching subtest of the Montreal-Toulouse-86 procedure (Nespoulous et al., 1992) was below normal (38.9 ± 5.07; normal 44.6 ± 2.19). The patients had a mean age of 35.1 years (± 8.4) and a mean of 13.4 years (± 4.7) of education. All patients were right-handed and native French speakers.

We also included 15 healthy controls to determine normal performance levels for the three behavioral tasks, thereby making it possible to characterize the syntactic deficits in the patients. These controls were not studied further. They were matched with patients for handedness (all right-handed), sex (10 men and 5 women), age 35.9 years (± 6.1), and number of years of education (13.7 ± 5.8; all F values < 1). The controls had no history of neurological or psychiatric disorders, and all were native French speakers. All control subjects performed normally during syntactic testing with the Montreal-Toulouse-86 procedure (Nespoulous et al., 1992).

Finally, we included 12 additional healthy adults from a cohort described elsewhere (Rosso et al., 2014), and in whom all the subsequent experimental steps were performed, including fiber-tracking, the calculation of tract overlaps with the patients' VLSM clusters, and correlation analyses between tract lesion load and syntax scores. These controls were matched with the first 15 controls for handedness, age, sex, and number of years of education (all F values < 1). Like the first 15 controls, none had language disorders and all had normal scores on the Montreal-Toulouse-86 procedure, indicating that they were suitable for tracking representative language/syntax tracts. All 12 subjects in this control group were native French speakers. We furthermore ensured that the control group was of high quality by matching each of the 12 subjects, one-to-one, with the 12 patients for handedness (all right--handed), sex (8 men and 4 women), age (34.4 years $\pm$ 12.7; $F < 1$) and number of years of education (13.5 ± 5.2; $F < 1$). Written informed consent was obtained from all participants.

Behavioral Tasks

The 12 patients and the 15 healthy controls completed three tasks relating to phrasal syntax and morphosyntax. These tasks have been used in patients with Huntington's

disease and have shown to display excellent sensitivity to striatal damage (Teichmann et al., 2005, 2006). All subjects performed the tasks in the same order: (1) "phrasal syntax," (2) "morphosyntax—production," and (3) "morphosyntax—perception."

Task 1: Phrasal Syntax

Syntactic capacities of sentence comprehension were assessed through a sentence-picture matching task that contrasted noncanonical (passives, object-relatives) and canonical sentences (actives, subject-relatives). These four types of stimuli have been used in previous studies and have generated important insight in the syntactic behavior of aphasic patients (e.g., Caplan et al., 1985). The processing of noncanonical structures, which demonstrate an "inverted" word order (e.g., complement before subject), depends on complex computations of "word-reordering," sometimes referred to as "transformational movement" (e.g., Grodzinsky, 2000; Jackendoff, 2002). By contrast, canonical structures can be processed on the basis of linear word-order information, involving more elementary computations sometimes referred to as "syntactic formation rules" (Jackendoff, 2002). For each of the two sentence types, we also manipulated the plausibility of the clauses to vary semantic factors potentially contributing to sentence comprehension in syntax-impaired patients. This approach yielded four types of sentences, namely plausible canonicals (e.g., "La fille arrose la fleur qui est blanche" [The girl waters the flower, which is white]; $N = 4$), nonplausible canonicals (e.g., "La fleur arrose la fille qui est blanche" [The flower waters the girl, who is white]; $N = 4$), plausible noncanonicals (e.g., "La fleur est arrosée par la fille qui est blanche" [The flower is watered by the girl, who is white]; $N = 4$), and nonplausible noncanonicals (e.g., "La fille est arrosée par la fleur qui est blanche" [The girl is watered by the flower, which is white]; $N = 4$). Two of the sentences of each condition were actives/passive structures whereas the other two were subject/object relative structures. Finally, each of the 16 sentences was paired once with a picture depicting the plausible version of the sentence (e.g., "a girl watering a flower") and once with a picture of the nonplausible version (e.g., "a flower watering a girl"). In summary, we used 32 sentence-picture pairs which were obtained by crossing three factors (canonicity, plausibility, structure), and which contained the same number of frequency-matched content words. Participants were asked to determine whether the auditorily presented sentence and the simultaneously presented picture were correctly matched (YES/NO answers). The sentences were recorded with a regular speech rate and neutral prosody; they were played through headphones at the same time as the picture appeared on the computer screen. Presentation order of the sentence-picture pairs was randomized. Based on published findings showing that lesions to Broca's area and the striatum lead to syntactic difficulties with noncanonical sentences (e.g., Kaan and Swaab, 2002; Santi and Grodzinski, 2007; Teichmann et al., 2008a, 2008b) we expected the patient group to have predominant deficits with sentences of this type, regardless of their structure (relatives vs. nonrelatives) and semantic aspects (plausibles vs. nonplausibles).

Finally, given the possible interaction between performance with sentences, particularly for noncanonical structures, and short-term memory, we also assessed forward and backward digit span in all subjects.

Task 2: Morphosyntax—Production

We assessed morphosyntactic processes through verb inflection, as, in most models, inflected words are considered to be the only complex forms for which combinatorial computations take place (e.g., Caramazza et al., 1988; Niemi et al., 1994). Such computations were assessed through the conjugation of nonce-verbs (NV) which, by definition, have no lexical representation and therefore specifically depend on combinatorial operations ([inflected form] = [root] + [suffix]). The assessment was refined by using two types of NV that were constructed following the main regularity of the French conjugation system pertaining to verbs ending in "-er" (e.g., *arriver—il arrive—il arrivera* [to arrive—he arrives—he will arrive]) and following less frequent regularities pertaining to verbs ending in "-ir" (e.g., *finir—il finit—il finira* (to finish—he finishes—he will finish). The two types of NV are, respectively, referred to here as "regular NV" (e.g., "*garouster*") and "subregular NV" (e.g., "*saronir*"). Combinatorial morphosyntax was contrasted with lexical-based verb inflection as required for the inflection of irregular and high-frequency regular verbs (Pinker and Ullman, 2002; Schreuder and Baayen, 1995).

Altogether, the materials contained 24 irregular verbs (mean frequency 181 per million ± 79), 24 high-frequency regular verbs (mean frequency 132 per million ± 53), 24 regular NV, and 20 subregular NV. The NV stimuli were constructed by changing two phonemes of the roots of existing verbs ending in "-er" (regular NV) and of existing verbs ending in "-ir" (subregular NV), while checking for the absence of phonological neighbors. All NV consisted of orthographically and phonotactically legal letter strings. Regular and irregular verbs were matched for the number of phonemes ($F < 1$) and for their log-transformed frequencies ($F < 1$) according to the LEXIQUE 2 database (New et al., 2004). Regular and subregular NV were also matched for the number of phonemes ($F < 1$). Subjects were asked to conjugate the stimuli in the present and in the future tense (third person singular) upon auditory presentation of the infinitive form by a trained speaker (e.g., *arriver; aujourd'hui il ___, demain il ___*" [to arrive, today he ___, tomorrow he ___"]). The stimuli were randomized within the two verb and within the two NV conditions. According to previous findings that damage to Broca's

area and the striatum leads to an impairment of combinatorial morphosyntax (Teichmann et al., 2005; Tyler et al., 2005; Vannest et al., 2005) we predicted that the patients would have specific difficulties with NV conjugation. Furthermore, given that subregular NV are likely to impose greater constraints on the morphosyntactic parser than regular NV, we expected patients to perform less well with subregular than with regular NV.

Task 3: Morphosyntax—Perception

This task was similar to Task 2, except that participants made right/wrong judgements on auditorily presented verb and NV forms (present and future tense, third person singular). For each item, we presented a correctly conjugated form (e.g., *garouster, aujourd'hui il 'garouste'* [today he...], *demain il 'garoustera'* [tomorrow he ...]) and several incorrectly suffixed forms. The items were prerecorded and then played back through headphones. By analogy to conjugation errors in Huntington's disease patients with striatal damage (Teichmann et al., 2005), the error forms corresponded either to the use of non-existing suffixes (aberrant suffixations; e.g., garouster—garouste*dra*), to the excessive use of the main conjugation regularity (over-regularizations; e.g., saronir—saron*era* instead of saron*ira*; double suffixations, e.g., garouster—garoust*erera*) or to the excessive use of conjugation subregularities (subregularizations; e.g., garouster—garoust*ira*). In total, the materials contained 27 irregular verb forms (2 correct and 7 error forms per item, mean frequency 173 per million ± 78), 21 regular verbs forms (2 correct and 5 error forms per item, mean frequency 125 per million ± 71), 21 regular NV (2 correct and 5 error forms per item), and 21 subregular NV (2 correct and 5 error forms per item). Regular and irregular verbs were matched for the number of phonemes ($F < 1$) and for their log-transformed frequencies ($F < 1$). Regular and subregular NV were matched for the number of phonemes ($F < 1$). Furthermore, irregular and regular verbs of Tasks 2 and 3 were frequency-matched (both F values < 1), and regular and subregular NV of Tasks 2 and 3 were matched for the number of phonemes (both F values < 1). The stimuli were randomized within the two verb and within the two NV conditions. As in Task 2, we predicted that the patients with frontal/striatal damage would have specific difficulties with NV inflection, which should predominate for subregular NV.

Lesion Analysis and Voxel-Based Lesion-Symptom Mapping

All patients underwent MRI less than 2 months before performing the behavioral tasks. Scans included three-dimensional (3D) T1-weighted images (inversion recovery-fast spoiled gradient echo; field of view = 250 mm^2; acquisition matrix = 288 × 256; voxel resolution = 0.5 × 0.5 × 1.2 mm^3; slice thickness = 1.2 mm) and were obtained with a 3T scanner (General Electric, HD23, France) with a standard head coil for signal reception. Lesion analysis was based on 3D T1-weighted images. Lesions were reconstructed on normalized templates (SPM8, http://www.fil.ion.ucl.ac.uk/spm) using an automatic segmentation method. This method was based on symmetry analysis (Colliot et al., 2004), mathematical morphology (Bloch, 2008), and geodesic active contours (Atif et al., 2006). Reconstructions were checked by a board-certified neurologist who was experienced in the use of these templates and blind to the behavioral deficits of the patients. For each patient, a lesion mask image in Montreal Neurological Institute space (MNI) was saved for voxel-based lesion-symptom mapping (VLSM), in which each voxel was labeled either 0 (intact) or 1 (lesioned). VLSM analysis (Bates et al., 2003) was conducted with Voxbo imaging-analysis software (www.voxbo.org) assessing the relationship between behavioral performance and brain damage voxel-by-voxel. Behavioral scores (dependent variable) were compared, at each voxel, between patients with and without lesions at that voxel (independent variable), in t-tests. This led to the generation of a statistical map of brain areas for which injury significantly impaired performance. The effects of outlier observations were minimized by including only voxels for which lesions were observed in at least two patients. Statistical maps were thresholded at $q < 0.05$ with a false discovery rate (FDR) of 0.05 to correct for multiple comparisons (Genovese et al., 2002). In VLSM, the power to detect brain-behavior relationships at a given voxel depends on the number of patients in the "lesioned" and "unlesioned" groups. Ideally, there should be equal numbers in the two groups (in the current dataset, six lesioned and six unlesioned for a given voxel). The lesion overlap map for the entire patient sample (Fig. 1) showed coverage to be good in the IPFC, the striatum and the intervening white matter region expected to contain the Broca-striatum syntax pathway. Concerning the striatum we also calculated the lesion volume overlap with both the caudate and the putamen. Overlap for the entire patient group was considerable with the caudate (23% ± 26) whereas it was small with the putamen (4% ± 3).

Fiber Tracking

Twelve healthy participants underwent MRI using a 3T scanner (VERIO system, SIEMENS, Germany) with a 32-channel head coil. The protocol included anatomical 3D T1-weighted *MPRAGE* images (magnetization prepared rapid acquisition gradient echo; TR = 2.3 s; TE = 4.18 ms; flip angle = 9°; TI = 900 ms; voxel size = 1 × 1 × 1 mm^3; 176 slices), and spin-echo echo-planar diffusion acquisition (TR = 10 s, TE = 87 ms, voxel size = 2 × 2 × 2 mm^3, 60 slices, 60 gradient-encoded directions with a b value of 1500s/mm^2, 11 nondiffusion-weighted volumes, with cardiac gating). Probabilistic tractography (Behrens et al.,

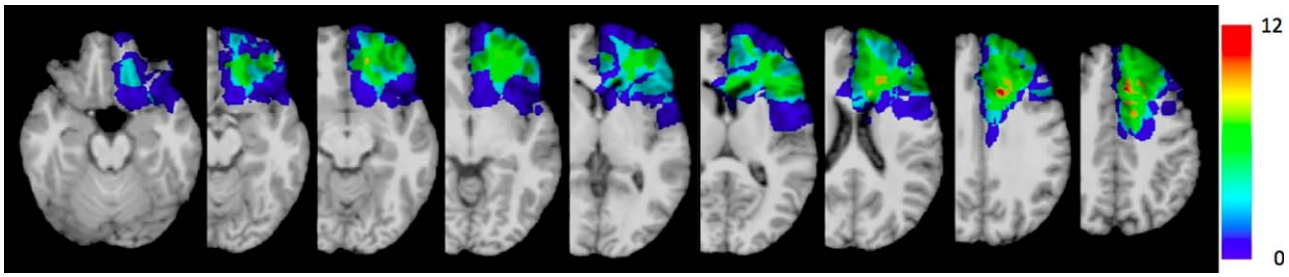

Figure 1.
Overlay of the lesions of all the patients ($N = 12$). Warmer colors indicate areas of greater lesion overlap, with 'green' corresponding to an ideal 'half-lesioned/half-unlesioned' distribution. Axial slices are shown in accordance with neurological convention (left is left).

2007) was used to reconstruct the fiber tracts shown to impact syntactic processing: the left arcuate fasciculus, the inferior frontooccipital fasciculus from the extreme capsule fiber system and the uncinate fasciculus. We also reconstructed the recently identified aslant tract that connects the supplementary motor area and Broca's area (Catani et al., 2012; Ford et al., 2010; Lawes et al., 2008; Oishi et al., 2008) and that is also involved in language processing (Catani et al., 2013). Finally, we tracked the putative Broca-striatum tract, based on the previous description of a fiber bundle linking Broca's area and the striatum (Lehéricy et al., 2004), and guided by our cortical and striatal VSLM results. Images were processed with FSL software (FMRIB Software Library; version 3.3; http://www.fmrib.ox.ac.uk/fsl). Diffusion images were corrected for eddy current distortions. Fractional anisotropy (FA) maps were generated with FDT (FMRIB's Diffusion Toolbox). The probabilistic distributions of the fiber orientations were calculated for each voxel with a constrained spherical deconvolution model and MRTRIX software (Tournier et al., 2004, 2007). Whole-brain probabilistic tractography was performed in the native space of each participant, by specifying the white matter map provided by segmentation of the T1-weighted image as the seed and the whole brain as the target. The regions of interest (ROIs) extracted from the "anatomical automatic labelling template" (version vbeta1, GYN, UMR6095, CYCERON, Caen, France) were then used to reconstruct the tracts of interest. The ROIs were Broca's area (BA44/45), the superior temporal gyrus, the supplementary motor area, the medial inferior frontal cortex, the external/extreme capsule, the inferior occipital region and the caudate nucleus. These ROIs were denormalized from the MNI space to the individual's non-weighted b0 image subject-by-subject, with the VBM8 toolbox (SPM, http://www.fil.ion.ucl.ac.uk/spm). For the arcuate fasciculus, we used Broca's area and the superior temporal gyrus as inclusion masks and the external capsule and the midsagittal plane as exclusion masks. For the uncinate, the external/extreme capsule, the medial inferior frontal region and the anterior temporal lobe were the inclusion masks. For the inferior frontooccipital fasciculus, the external/extreme capsule and the inferior occipital cortex were the ROI's. For the aslant, Broca's area and the supplementary motor area were used as inclusion masks. Concerning the Broca-striatum tract, the inclusion masks derived from our VLSM results were Broca's area and the caudate nucleus.

Probabilistic templates were constructed by normalizing each tract from each participant in the MNI space, with the transformation matrix derived from the anatomical images. We averaged each tract across subjects, with the ImCalc function of SPM8 (http://www.fil.ion.ucl.ac.uk/spm/). The probability tract template was then thresholded at 10% of the maximum probability (Heiervang et al., 2006), and anatomically plausible tracts without aberrant fibers were identified by visual checking. Finally, each of the five template tracts was re-sliced with the normalized images of the binary segmented lesions from the 12 patients.

Tract/VSLM Overlap, Tract Lesion Load, and Correlation Analyses With Syntax

We determined the overlap of each tract with the VLSM voxel clusters linking the IPFC and the striatum, by calculating the intersection between each of the five tracts and the VLSM clusters, and dividing by the total number of voxels of each tract. We then determined the lesion load of each tract by calculating the overlap between the anatomical lesions of each patient and the different tract templates. We used the formula "lesion load = $N_{overlap}/N_{tract}$" where $N_{overlap}$ is the number of voxels in the intersection between the lesions and the template tracts and N_{tract} is the total number of voxels in the tract concerned. Finally, we ran correlation analyses using for each tract the lesion load of the 12 patients and their syntax scores. Bonferroni-correction for multiple comparisons was applied.

RESULTS

Behavioral Results

Analyses of variance (ANOVAs) were performed by participants ($F1$) and by items ($F2$) on the performance of the 12

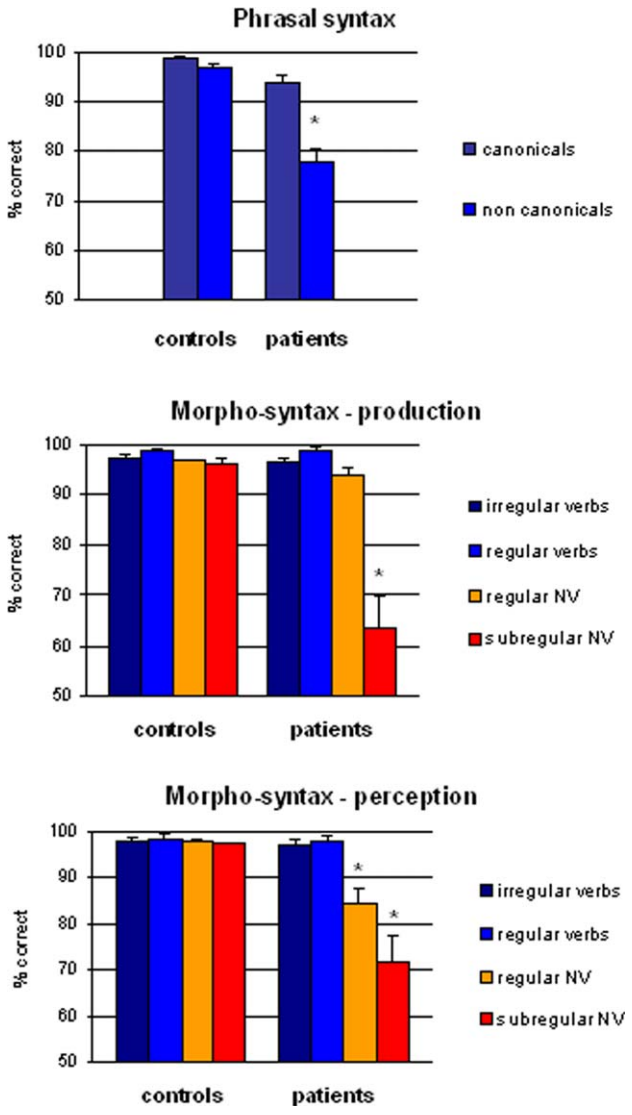

Figure 2.
Performance of patients and healthy controls in the three syntax tasks.

patients and the 15 healthy controls. For the three experimental tasks the independent variables were group (patients, controls) and stimulus type, and the dependent variable was accuracy. The results are summarized in Figure 2.

Task 1: Phrasal Syntax

The three independent variables were "canonicity" (canonical, noncanonical), "plausibility" (plausible, nonplausible) and "structure" (actives/passives, subject/object relatives). A global ANOVA showed poorer performance in patients (85.68 ± 18.76) than in controls [$97.71\% \pm 7.24$; $F1(1,25) = 34.383$, $P < 0.001$; $F2(1,24) = 34.140$, $P < 0.001$]. We found an effect of canonicity [$F1(1,25) = 25.946$, $P < 0.001$; $F2(1,24) = 16.738$, $P < 0.001$] and a significant group × canonicity interaction $F1(1,25) = 18.243$, $P < 0.001$; $F2(1,24) = 11.660$, $P = 0.002$], but no effect of plausibility [$F1(1,25) = 1.588$, $P = 0.219$; $F2 < 1$] or sentence structure ($F1 < 1$, $F2$) and no interaction between group and these two variables (both $F1 < 1$; both $F2 < 1$). The group × canonicity interaction was due to the fact that patients had poorer performance with noncanonical ($77.6\% \pm 21.4$) than with canonical sentences [$93.8\% \pm 10.9$; $F1(1,11) = 21.530$, $P = 0.001$; $F2(1,24) = 15.584$, $P = 0.001$] whereas controls performed equally well with canonical (98.75 ± 5.5) and noncanonical sentences [96.7 ± 8.6; $F1(1,14) = 4.375$, $P = 0.055$; $F2(1,24) = 2.586$, $P = 0.121$]. Finally, comparing patients and controls showed that performance with canonical sentences was also slightly impaired in the patient group [$F1(1,25) = 12.698$, $P = 0.002$; $F2(1,15) = 5.217$, $P = 0.037$]. In a second step, we checked whether the poor outcome with noncanonical sentences would reflect deficits of verbal short-term memory rather than syntactic failure *per se*. Digit span assessment showed that short-term memory capacities were only slightly lower in patients than in controls (forward span 6.8 ± 2.7, backward span 4.1 ± 2.9; controls: forward span 7.5 ± 1.7, backward span 4.9 ± 2.1). No significant correlation was found between digit span scores and syntactic scores for noncanonical sentences in the 12 patients (forward span: $R = 0.32$, $P > 0.1$; backward span: $R = 0.37$, $P > 0.1$).

Tasks 2 and 3: Morphosyntax Production and Perception

We used "stimulus type" as independent variable (irregular verbs, regular verbs, regular NV, and subregular NV). In the production task (Task 2) performance was poorer in patients ($88.2\% \pm 18.3$) than in controls [97.3 ± 3.1 ($F1(1,25) = 36.917$, $P < 0.001$; $F2(1,88) = 73.462$, $P < 0.001$]. There was an effect of stimulus type [$F1(3,75) = 26.205$, $P < 0.001$; $F2(3,88) = 44.604$, $P < 0.001$] and a significant group × stimulus-type interaction [$F1(3,75) = 26.782$, $P < 0.001$; $F2(3,88) = 64.334$, $P < 0.001$]. This interaction was due to the similar performances of the controls for the four types of stimuli [$F1(3,42) = 2.361$, $P = 0.085$; $F2 < 1$), whereas performance differed between stimulus types for patients [irregular verbs, $96.53\% \pm 3.48$ correct; regular verbs, $98.96\% \pm 2.59$ correct; regular NV, $94.10\% \pm 4.52$ correct; subregular NVs, 63.33 ± 21.98 correct; $F1(3,33) = 24.802$, $P < 0.001$; $F2(3,88) = 67.184$, $P < 0.001$]. Restricted analyses showed that patients performed less well than controls only with subregular NV [$F1(1,25) = 32.181$, $P < 0.001$; $F2(1,19) = 92.514$, $P < 0.001$] whereas performance was similar with regular NV [$F1(1,25) = 4.138$, $P = 0.053$; $F2(1,23) = 3.488$, $P = 0.075$], irregular verbs ($F1 < 1$; $F2 < 1$) and regular verbs ($F < 1$; $F2 < 1$).

In the perception task (Task 3) patients also performed less well ($87.82\% \pm 15.77$ correct) than controls [97.8 ± 2.44, $F1(1,25) = 33.693$, $P < 0.001$; $F2(1,86) = 57.978$, $P < 0.001$].

There was an effect of stimulus type [$F1(3,75) = 26.205$, $P < 0.001$; $F2(3,75) = 14.545$, $P < 0.001$] and a significant group × stimulus-type interaction [$F1(3,75) = 15.087$, $P < 0.001$; $F2(3,86) = 22.210$, $P < 0.001$]. This interaction was due to the fact that controls had similar performance for the four stimulus types [$F1(3,42) = 1.002$, $P = 0.401$; $F2 < 1$], whereas there were differences for patients [irregular verbs 96.91% ± 4.42 correct, regular verbs 98.02% ± 3.78 correct, regular NV 84.52% ± 11.14 correct, subregular NV 71.83 ± 20.25 correct; $F1(3,33) = 13.533$, $P < 0.001$; $F2(3,86) = 29.515$, $P < 0.001$]. Restricted analyses showed that patients performed less well than controls with both subregular NV [$F1(1,25) = 23.263$, $P < 0.001$; $F2(1,20) = 35.432$, $P < 0.001$] and regular NV [$F1(1,25) = 20.180$, $P < 0.001$; $F2(1,20) = 26.536$, $P < 0.001$] but similarly to controls with irregular verbs ($F1 < 1$; $F2 < 1$) and regular verbs ($F < 1$; $F2 < 1$). Finally, comparing the two NV types in patients showed that performance was poorer with subregular than with regular NV [$F1(1,11) = 9.143$, $P = 0.012$; $F2(1,40) = 7.769$, $P = 0.008$].

VLSM Results

Several frontal–cortical and subcortical regions were found to have a significant impact on behavioral scores in VLSM analyses ($P < 0.05$). In particular, syntactic and morphosyntactic performance, as assessed with noncanonical sentences and subregular NV, was associated with voxels of a region extending from the left IPFC (BA44, BA45, rostrally adjacent areas of BA47), throughout the intervening white matter, to the caudate head of the left striatum (see Fig. 3). The largest number of voxels ($P < 0.05$) was found in BA45 with 9429 voxels for noncanonical sentences, 4278 voxels for subregular NV during production and 7335 voxels for subregular NV during perception. These three continuous and largely overlapping voxel bundles strongly suggested the existence of a Broca-caudate pathway dedicated to particular aspects of syntax. By contrast, performance with regular NV in production and perception was associated with two topographically separated voxel clusters including Broca's area (BA44/45) and left caudate head, respectively. Performance with canonical sentences involved a voxel cluster of BA44/45 that extended caudally to the underlying white matter, with no involvement of the deep white matter regions or the caudate. Finally, lexical access to irregular and high-frequency regular verbs was not associated with any of the lesioned voxels in our patient sample, for either the production or the perception task.

Fiber Tracking, Tract/VLSM Overlap, and Correlation Analyses

Fiber tracking identified the arcuate (volume 6.9 $cm^3 \pm 1.8$), the inferior frontal–occipital fasciculus of the extreme capsule fiber system (volume 5.8 $cm^3 \pm 2.8$), the uncinate (volume 4.3 $cm^3 \pm 2.3$), and the aslant (volume 17.9 $cm^3 \pm 7.3$), the trajectories of which were consistent with published findings of the anatomical literature (Catani et al., 2002, 2005, 2012; Frey et al., 2008; Ford et al., 2010; Glasser and Rilling, 2008). It also identified a Broca-striatum tract (volume 15.7 $cm^3 \pm 6.8$) connecting BA45 and the left caudate head, tracing a direct trajectory through the anterior portion of the internal capsule. This tract, consistent with the anatomical findings of Lehéricy et al. (2004), is hereafter referred to as the "Broca-caudate tract." To investigate whether the Broca-caudate tract plays a genuine role in syntax we checked (1) its overlap with the three syntax-related VLSM voxel clusters linked to noncanonical sentences and subregular NV and (2) whether its lesion load in the 12 patients is correlated with the patients' syntax scores. The anatomical overlap was considerable for this tract (noncanonicals 41%, subregular NV production 32%, subregular NV perception 43%) but small for the four other tracts (all <20%; see Fig. 4). Furthermore, the lesion load values of the Broca-caudate tract (mean 19% ± 22) were correlated with performance for noncanonical sentences ($R = 0.778$, $P = 0.003$) and subregular NV in production ($R = 0.808$, $P = 0.001$) and perception ($R = 0.804$, $P = 0.002$). By contrast, no significant correlation was found for canonical sentences or for regular NV, suggesting that the Broca-caudate tract plays a specific role in syntax. Furthermore, the arcuate (mean lesion load 6% ± 8) was significantly correlated with performance for canonical sentences ($R = 0.831$, $P = 0.001$) whereas no correlation was found for the uncinate fasciculus (mean lesion load 12% ± 20), the inferior frontooccipital fasciculus (mean lesion load 6% ± 9), or the aslant (mean lesion load 24% ± 13). The results of the correlation analyses for the Broca-caudate tract are illustrated in Figure 5.

DISCUSSION

We used a systematic stepwise approach to explore whether, in addition to the known cortico-cortical routes, the syntax network also includes a deep frontostriatum pathway accounting for the impact of the striatum on syntactic processing. Our unique combination of syntactic assessments and multimodal imaging revealed the existence of a Broca-caudate pathway linking BA45 with the left caudate head and affecting core aspects of complex syntax.

The syntactic assessments showed that the patients with frontal/striatal damage displayed impairment of both phrasal syntax and verbal morphosyntax. They displayed impairment specifically for noncanonical sentences, which was independent of semantic factors (plausibles vs. nonplausibles) and sentence structure (relatives vs. nonrelatives). This pattern suggests a particular failure of syntax affecting transformational operations of "word reordering" whereas the processing of canonical or of relative structures remains largely intact. The kind of specificity within the domain of syntax itself indicated that the task

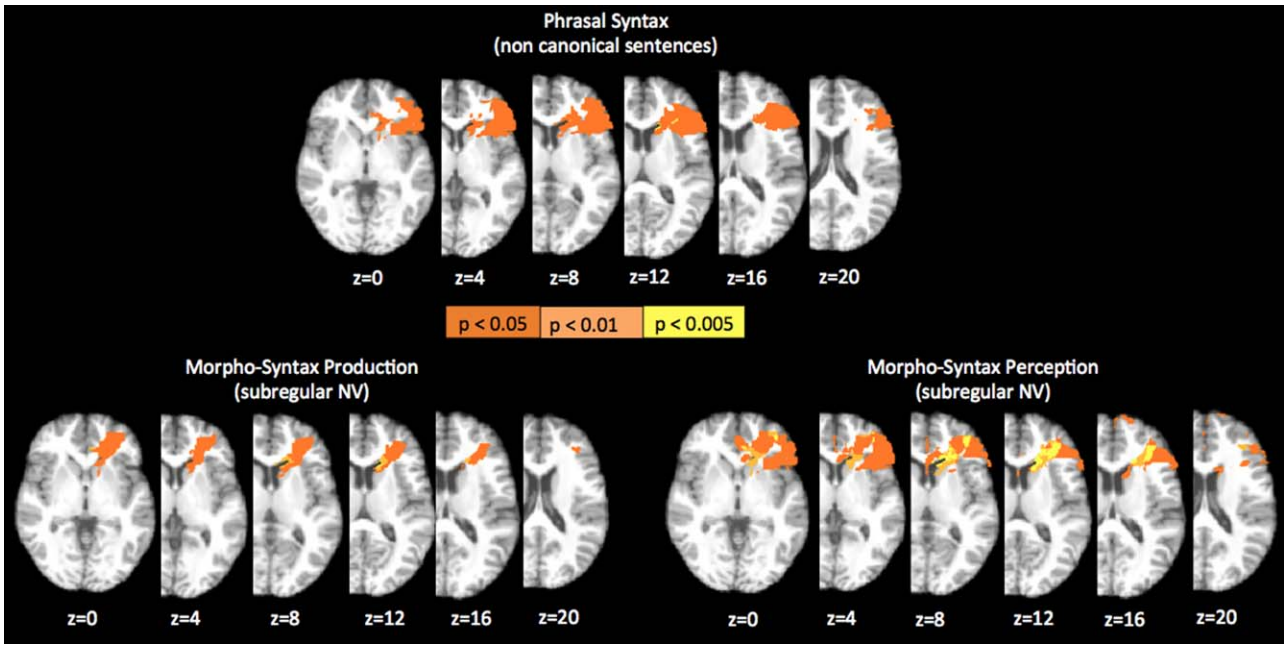

Figure 3.

VLSM data showing voxels critically involved in performance for phrasal syntax (noncanonical sentences) and verbal morphosyntax (subregular NV). The voxels formed bundle-like clusters extending from the IPFC (BA44, 45, 47) to the left caudate head. Regions modulating task performance are indicated in dark orange ($P < 0.05$), light orange ($P < 0.01$), and yellow ($P < 0.005$) on axial MRI slices corresponding to the MNI coordinates $z = 0$, $z = 4$, $z = 8$, $z = 12$, $z = 16$, and $z = 20$. Slices are shown in accordance with neurological convention (left is left).

genuinely tapped particular aspects of syntactic processing, which will be important for subsequent tract-function considerations. Moreover, given that the processing of complex sentences may also be dependent on verbal short-term memory (e.g., Caplan and Waters, 1999; Fiebach et al., 2005; Makuuchi et al., 2009) we assessed the correlation between the patients' performance for noncanonical sentences and their forward and backward digit spans. No correlations were found indicating that general working memory deficits can hardly explain the syntactic failure in these patients. Tasks 2 and 3 showed that the syntactic impairment extended to combinatorial morphosyntax as reflected by the impaired inflection of NV and the preservation of lexical access to irregular and high-frequency regular verbs. This deficit predominantly affected subregular NV, which presumably place higher constraints on the syntactic parser, and concerned both production and perception, thus localising the impairment at a modality-independent level of morphosyntax.

We then used VLSM, combining syntactic data with the patterns of lesions in patients, to obtain a global approximation of the frontostriatal syntax pathway. We identified three bundle-like voxel clusters extending between BA44/45/caudal BA47 and the left caudate head as significantly involved in the phrasal syntax of noncanonical sentences and in the morphosyntax of inflectional subregularities. Fiber-tracking in healthy participants confirmed the existence of a "BA45-caudate head" tract which overlapped with these VLSM clusters, suggesting that this tract, in its entirety, has a specific impact on the processing of complex syntax and morphosyntax. By contrast, no substantial VLSM overlap was observed for the cortico-cortical tracts thought to affect syntactic processes, namely the dorsal route of the arcuate, the ventral route of the extreme capsule fiber system / inferior frontooccipital fasciculus and the uncinate (Friederici et al., 2006; Griffiths et al., 2013; Wilson et al., 2011). Likewise, no substantial overlap was observed for the aslant tract, for which Catani et al. (2013) suggested a role in lexical fluency and which was considered to be a syntax-unrelated control tract. Finally, analysis of the correlation of lesion load with syntactic impairment, for each tract and for the whole group of patients, confirmed that only the Broca-caudate tract had a significant impact on complex syntax processing for both noncanonical sentences and inflectional subregularities. The results of our correlation analyses were also consistent with the syntactic function of the arcuate fasciculus (e.g., Friederici, 2009; Wilson et al., 2011), which was found to have an impact on canonical sentence structures, which are more frequently used in common language than noncanonical structures. Finally, the aslant which was used as a control tract encompassing, as the Broca-caudate tract, cortical

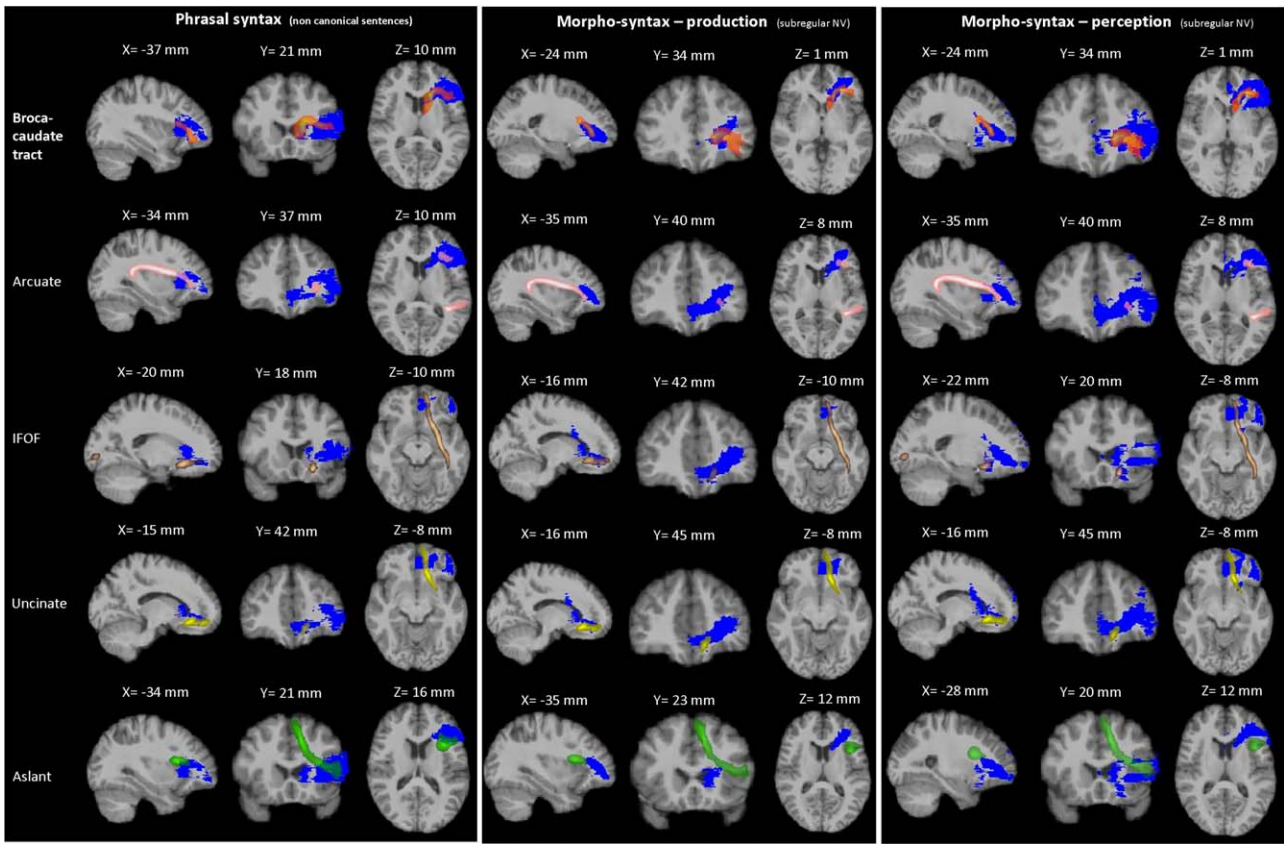

Figure 4.

Fiber tracking results for the Broca-caudate tract (orange), the arcuate (pink), the inferior frontooccipital fasciculus (IFOF) of the extreme capsule fiber system (light brown), the uncinate (yellow) and the aslant (green). The five tracts are overlaid on the three VLSM voxel clusters (blue) playing a critical role in the processing of phrasal syntax (noncanonical sentences) and morphosyntax (subregular NV in production and perception). MNI coordinates correspond to the brain sections with the largest overlap between VLSM clusters and the various tracts. Slices are shown in accordance with neurological convention (left is left).

zones of Broca's area, yielded no significant correlation. Thus it appears that the processing of complex syntax is not dependent solely on local computation within the Broca cortex, instead involving an integrative network including the entire Broca-caudate tract. Altogether, the data show that the Broca-caudate pathway is separate from the known language tracts, that it plays a specific role in syntax, and that its disruption causes damage to the processing of complex syntax.

Integration of the Broca-Caudate Pathway into Current Network Models of Syntax

Our findings provide both new elements for current models of brain-syntax networks and support for previous findings relating to cortico-cortical pathways. They confirm the many claims that the arcuate fasciculus plays a key role in the processing of common sentences structures (Friederici, 2009; Griffiths et al., 2013; Wilson et al., 2011) and they are consistent with the finding that the aslant tract, which affects lexical-related processes (Catani at al., 2013), has no particular function in syntax. Furthermore, consistent with the findings of Wilson et al. (2011), they indicate the absence of a role in syntax of the ventral extreme capsule fiber system and, more particularly, of the inferior frontooccipital fasciculus, which has been suggested to contribute to semantic processing (Duffau et al., 2005). In addition, our findings reveal the existence of a "novel" cortico-subcortical syntax pathway thus enriching current models (e.g., Friederici, 2009; Kaan and Swaab; 2002) through the integration of the deep gray matter of the striatum, which plays a major role in syntactic processes (Friederici et al., 2003; Moro et al., 2001; Newman et al., 2010; Teichmann et al., 2005, 2008a, 2008b). How is the Broca-caudate tract related to other Broca pathways? Various tracts linking Broca's area to medial-frontal (e.g., Ford et al., 2010), parietal and temporal cortices (e.g., Frey

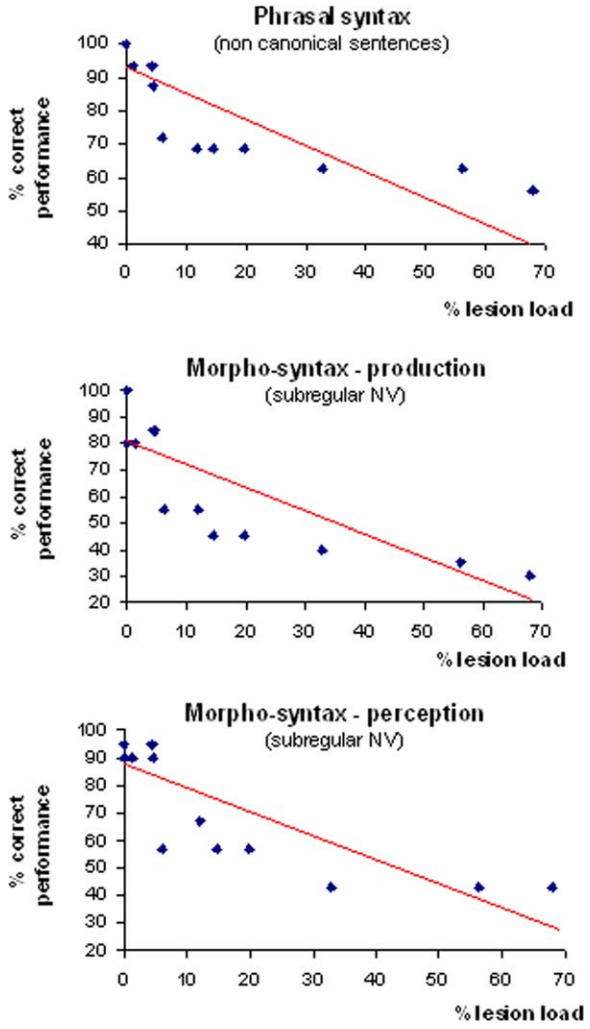

Figure 5.
Correlation between lesion load values for the Broca-caudate tract and phrasal syntax and morphosyntax scores for the 12 patients.

et al., 2008; Glasser and Rilling, 2008), and to subcortical structures, such as the putamen and thalamus (e.g., Croxson et al., 2005; Draganski et al.; 2008; Ford et al., 2013), have been identified by tracking studies. However, with the exception of the arcuate, the linguistic role of the tracts identified remains unclear because these studies did not use experimentally generated language data. Investigations combining tracking with language assessment would be of particular interest here for tracts connecting Broca's area to the putamen or thalamus, given that the caudate-putamen-thalamus complex forms a tightly interconnected network within the basal ganglia loops. However, our VLSM analyses identified voxel clusters only in the caudate, and subsequent fiber tracking was consistently guided by this anatomical localization. Nevertheless, the investigation of a putative syntax role of Broca-putamen and thalamus-Broca tracts will be an important topic for future research, beyond the scope of the work reported here.

Our behavioral and correlation results also provide some clues to the syntactic role of the Broca-caudate tract, by indicating its involvement in complex computations required for transformational word-reordering in sentences and for the processing of subregularities during verb inflection. Such a function is consistent with previous findings that the endpoints of the Broca-caudate tract, namely Broca's area and the left striatum, contribute to both the processing of noncanonical structures and rule-based conjugation (Ben-Shachar et al., 2003; Kaan and Swaab, 2002; McNamara et al., 1996; Santi and Grodzinski, 2007; Teichmann et al., 2005, 2008a, 2008b; Tyler et al., 2005; Vannest et al., 2005). However, the Broca-caudate tract is probably not the only pathway for such computations, but we propose that it functionally and anatomically extends other syntax pathways. Questions could be raised concerning the consistency of the function of the Broca-caudate pathway in complex syntax with findings assigning such a function to BA44 and the arcuate rather than to BA45 (e.g., Bahlmann et al., 2008; Bornkessel et al., 2005; Friederici, 2009). We suggest that these data are complementary rather than conflicting, and that the processing in the dorsal arcuate-BA44 pathway may require computational reinforcement from an additional processing step within the BA45-caudate pathway identified here. In accordance with this view, both BA44 and BA45 have been reported to be activated during tasks involving the manipulation of complex syntax (e.g., Ben-Shachar et al., 2003; Friederici et al., 2006; Musso et al., 2003; Santi and Grodzinski, 2007; Tyler et al., 2010, 2011).

The view of consecutive computations in a distributed arcuate-BA44–BA45-caudate network is also consistent with claims about the general role of the frontal–striatal circuitry in automating procedures and potentiating cortical input for the rapid and efficient execution of various mental operations (Graybiel, 1998; Redgrave et al., 2011; Wise et al., 1996). Accordingly, complex syntax computations are presumably initiated in the arcuate-BA44 network, with the additional reinforcement of automated syntactic procedures subsequently provided by the BA45-caudate pathway. This crosstalk between pathways, allowing complex computations that heavily draw on the syntactic parser, could be promoted by intrinsic Broca BA44-BA45 links, the existence of which has been substantiated by several neurobiological studies (e.g., Tardif et al., 2007). The view of the Broca-caudate pathway proposed here is also consistent with functional language accounts of the frontal–striatal circuitry, which is thought to underpin automated procedures of linguistic rule application ("declarative/procedural model"; Ullman, 2001). This model has been supported by several neuropsychological and imaging findings (e.g., Laine et al., 1999; Ullman et al., 1997; Vannest et al., 2005), leading to the prediction of a "grammar-related basal ganglia circuitry involving Broca's

area" (Ullman, 2006). Similarly, Dominey and coworkers have proposed a computational model simulating 'syntactic construction' based on recurrent fronto-striatal connections between BA44/45/47 and the caudate while assuming hypothetical Broca-striatal "grammar circuits" (Dominey et al., 2006; Dominey and Inui, 2009).

Limitations and Conclusion

The identification of a deep syntax pathway adds to the knowledge of cortico-cortical language networks and is consistent with models of frontostriatal circuits. Our findings are also consistent with previous fiber tracking studies revealing the existence of anatomical links between BA45 and the left caudate nucleus (Lehéricy et al., 2004). Furthermore, the "novel" Broca-caudate syntax pathway was indentified in a relatively small patient cohort, suggesting a high degree of anatomical and functional relevance.

This work is subject to some limitations and opens up new perspectives for research. First, we focused exclusively on the caudate, without studying other basal ganglia components, such as the putamen or thalamus, both of which have been shown to connect with Broca's area (Ford et al., 2013) and to affect syntactic performance (Friederici et al., 2003; Wahl et al., 2008). Future studies should address this issue by combining anatomical and linguistic explorations to elucidate the integrated cortical–subcortical circuitry, potentially computing syntactic information in the striatum-thalamus complex and conveying it back to Broca's cortex. It will be of particular interest to explore the linguistic role of Broca-putamen connections which might have been affected in our patient population given their anatomical proximity to the Broca-caudate tract (e.g., Lehéricy et al., 2004). Although the lesion-putamen overlap was only 4% in the patients, subcortical white matter lesions could have damaged Broca-putamen fibers potentially contributing to the syntactic impairment. Thus, despite the significant correlation between syntax function and the Broca-caudate tract, further research is needed to disentangle Broca-caudate and Broca-putamen connections and specify their respective roles in the processing of sentences and verbs. Second, difficulties inherent to tracking methods may lead to tract miss-identifications, particularly in volumes containing highly intertwined and crossed fibers, as in the region of the caudate–putamen–thalamus complex. However, we are confident that the Broca-caudate tract genuinely exists as we replicated findings from many anatomical studies demonstrating fiber connections between the prefrontal cortex and the caudate nucleus (e.g., Croxson et al., 2005; Leh et al., 2007; Lehéricy et al., 2004). Third, one could ask whether the use of two healthy control groups may have affected the scientific relevance of our findings, although we strongly believe that this is not the case. The two control groups were used to address different issues at different levels. The first was used exclusively to demonstrate syntactic disorders in patients, whereas the second group was used to address all subsequent anatomo-functional issues. Furthermore, the two healthy groups did not differ with respect to syntactic competency. Both had normal performance in the Montreal-Toulouse-86 procedure and were matched for age, sex, handedness and years of education. In addition, the syntax tasks used in this study have yielded invariably high scores in various groups of healthy adults (Teichmann et al., 2005, 2006, 2008). Finally, additional linguistic specification is required for the syntax function of the Broca-caudate tract and our findings require replication with different techniques, such as studies of the direct correlation between tract parameters and syntax scores, in both healthy adults and patients. The agrammatic variant of primary progressive aphasia is a potentially valuable model of graduated alteration of these parameters in the Broca-caudate tract. Using such correlations could improve our understanding of the Broca-caudate tract, its particular function in syntactic computation and its integration into the distributed network of frontostriatal-thalamic processing.

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