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Damage to the Frontal Aslant Tract accounts for visuo-constructive deficits in Alzheimer's Disease.

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Abstract

The Frontal Aslant Tract (FAT) has been described as a bundle connecting the Broca's area to the Supplementary Motor Area (SMA) and the pre-SMA in both hemispheres. The functional properties of this tract, and its role in degenerative dementia, such as Alzheimer's disease (AD) still need to be fully clarified. The aim of this study was to explore the microstructural integrity of the FAT in patients with AD and its potential relationship with cognitive functioning. Twenty-three patients with AD and 25 healthy subjects (HS) were enrolled. All subjects underwent cognitive and MRI examination. MRI including diffusion sequences was used for probabilistic tractography analysis. We reconstructed individual FATs bilaterally and assessed their microstructural integrity using fractional anisotropy (FA), computed as both, mean tract value and voxel-wise using SPM-8. Mean FA values were then used to test for correlations with cognitive measures. Mean tract FA and voxel-wise analyses revealed that patients with AD, compared to HS, had decreased FA in the FAT bilaterally. In addition, positive associations were found between FA in the FATs and patients' performance at tests for constructional praxis and visuo-spatial logical reasoning. The present results reveal a bilateral damage of FAT in AD patients. The association between FATs' microscopic abnormalities and constructive abilities fits well with the knowledge of a functional involvement of SMA and pre-SMA in movement sequences when executing constructive praxis tasks. The FAT is an associative bundle critically involved in the network sub-serving constructional praxis in patients with AD.

Keywords: Frontal Aslant Tract; Alzheimer's disease; visuo-spatial abilities; disconnection; tractography.

INTRODUCTION

Alzheimer's disease (AD) is currently recognized as the most common cause of dementia in the Western world [1]. In its typical form, AD presents with a distinct pattern of grey (GM) and white matter (WM) brain tissue damage [2], supporting the existence of a disconnection syndrome [2, 3] in addition to regional GM loss. Several previous studies used diffusion tensor imaging (DTI) to investigate the role of structural brain disconnection in AD at different clinical stages [4, 5].

DTI-based tractography allows single WM tracts to be segmented and assessed in their microscopic integrity, as previously demonstrated in patients with different forms of dementia, including AD. Subtle abnormalities have been demonstrated in several WM tracts of patients with AD, such as the uncinate fasciculus [6], the cingulum [7], the inferior and superior longitudinal fasciculus [8], and the corpus callosum [9]. The structural properties of all these tracts and their relationship with cognitive and non-cognitive symptoms have been extensively studied in patients with AD [10, 11]. More recently the frontal aslant tract (FAT) has been identified in normal brains [12]. FAT is a bundle connecting Broca's area (inferior frontal gyrus, BA44) to the anterior cingulate cortex (ACC, BA32), the Supplementary Motor Area (SMA, BA6), and the pre-SMA in both hemispheres [12]. It is known that FAT plays a role in normal language development, as previously shown in young healthy individuals [13]. There is also some evidence that FAT is involved in language impairments due to primary progressive aphasia (PPA) [14], brain tumors [15, 16, 17], and stroke [18]. FAT is considered as a part of a "motor stream" mainly involved in speech production [19] and complementing the dorsal and ventral language streams [20]. Microstructural abnormalities in several WM tracts have been described in AD brains [4, 6, 7], whose involvement is likely to affect broader networks. As previous studies demonstrated that SMA, pre-SMA, ACC and Broca's area (all connected by the FAT) are implicated in movement initialization and motor organization

[21, 22], we hypothesize here that damage to the FAT may induce widespread patterns of brain disconnection, affecting functions beyond language processing. In particular, we suppose that the network connected by the FAT may be relevant for cognitive functions requiring motor control and coordination, such as constructional praxis. Deficits of constructional praxis together with memory dysfunctions are commonly observed in AD since its early clinical stages [23, 24, 25]. Therefore, specific aim of the present study is investigate the extra-linguistic role of the FAT, mainly its possible involvement in the motor control and coordination. For this purpose we selected a cohort of typical AD patients in which language disabilities are not a key-features of the disease. The microstructural integrity of the FAT was correlated mainly with the constructional praxis abilities, and, such as control, with the other cognitive dysfunctions.

MATERIALS AND METHODS

Subjects

A cohort of 23 patients with the typical form of probable AD was recruited for the current study from the Specialist Dementia Clinic of the Catholic University of Rome (Rome, Italy). The diagnosis of probable AD was made according to the clinical criteria of the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [26]. To be included, patients had to meet the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria [27] for the diagnosis of major of neurocognitive disorders due to AD. All patients underwent an extensive neuropsychological battery and MRI scanning.

In order to improve the diagnostic accuracy, conventional T1-weighted images were clinically reviewed by using the Medial Temporal lobe Atrophy scale (MTA) [28] to include only patients with a MTA score ≥ 1.5 . This means that only patients with AD-due to AD at intermediate likelihood were included for the study (see Table 1).

Twenty-five healthy elderly subjects (HS) were also recruited and served as controls. They all reported scores within the range of normality at the Mini Mental State Examination (MMSE) [29] (Italian cut-off ≥ 23.8 ; [30]) and they had to show a MTA score ≤ 1 (see Table 1).

Subjects with a Hachinski score [31] higher than 5 were excluded.

Major systemic, psychiatric, vascular, and other neurological illnesses were carefully investigated and excluded in all patients and controls. ,

Finally, all participants had to be right-handed to be included in the present study.

The Ethical Committee of Santa Lucia Foundation approved the study and written informed consent was obtained from all participants before study initiation. All procedures performed in this study were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Neuropsychological assessment

All participants underwent a clinical interview to assess their linguistic abilities (spontaneous speech and comprehension) and an extensive neuropsychological battery covering most cognitive domains, which included: a) verbal episodic long-term memory: 15-Word List (Immediate and 15-min Delayed recall) [32]; b) working memory: Digit span backward [33]; c) executive functions: Phonological Word Fluency [32]; d) language: Naming objects subtest of the BADA (“Batteria per l’Analisi dei Deficit Afasici”, Italian for “Battery for the analysis of aphasic deficits”) [34]; e) reasoning: Raven’s Coloured Progressive Matrices [32]; f) constructional praxis: copy of simple drawings with and without landmarks [32]; g) general cognitive efficiency: Mini Mental State Examination (MMSE) [29, 30].

MRI acquisition

All subjects underwent an MRI examination at 3T (Magnetom Allegra, Siemens, Erlangen, Germany), including the following acquisitions: 1) dual-echo turbo spin echo [TSE] (TR = 6190 ms, TE = 12/109 ms); 2) fast-fluid attenuated inversion recovery (FLAIR) (TR = 8170 ms, TE = 96 ms, TI = 2100 ms); 3) 3D Modified Driven Equilibrium Fourier Transform (MDEFT) scan (TR = 1338 ms, TE = 2.4 ms, Matrix = 256x224, slices number = 176, thickness = 1 mm); 4) Diffusion tensor imaging (DTI) (TR = 7000 ms, TE = 85 ms, 61 diffusion directions, maximum b factor = 1000 smm^{-2} , isotropic resolution 2.3 mm^3).

DTI pre-processing and FAT tractography

Correction for eddy currents and small head movements was done on DTI volumes by means of affine registration to the first non-diffusion weighted volume using FSL (<http://fsl.fmrib.ox.ac.uk/> Smith et al., 2004). Fractional Anisotropy (FA) maps were obtained for each subject in native space using FSL [35] and CAMINO (<http://camino.cs.ucl.ac.uk/>). Probabilistic tractography was performed using PICO [36] to reconstruct the Frontal Aslant tract (FAT), in both right and left hemisphere. Seed-points and waypoints were defined manually on the coronal FA maps of each participant according to published guidelines [14] (see Figure 1). When defining seed and waypoints, the operator (G.B.G.) was blind about individual's brain scans belonging.

FA maps were warped to the FMRIB58_FA_1mm template in MNI space using Advanced Normalization Tools (ANTS, <http://stnava.github.io/ANTs/>) software. FAT maps were normalized using the same transformation.

Then, for each subject, in the bilateral FAT we used a threshold to include only voxels with a probability of connection > 10%. The threshold tracts were binarised to obtain a mask on the FAT for every subject. These masks were used to extract each subject's

mean FA on the FAT, bilaterally. Moreover, voxel count of each segmented FAT was used to assess the volumetric characteristics of each tract.

Voxel-wise analyses on FAT

Before running the voxel-wise analysis using SPM8 (<http://www.fil.ion.ucl.ac.uk/spm>), individual tracts of both groups (AD and HS) were merged and averaged to create a binarised mask for the right and left side. Then, this tracts' mask was used to restrict the analysis to the area of interest. A full-factorial design was used to investigate between-group differences. In addition, in AD patients only, correlations were employed to investigate potential associations between voxel-by-voxel FA of bilateral FAT and patients' performance at cognitive tests. To test for these associations, a series of one-sample T-test models were used with individual cognitive scores as a covariate of interest. In all analyses, individual volumes of the FAT were entered as a covariate of no interest.

Statistical analysis

One-way ANOVAs were employed to assess between group differences in the demographical and clinical characteristics.

Seven one-way ANOVAs were employed to assess the cognitive differences between patients with AD and HS. Bonferroni's correction was applied (p value threshold for significance was computed as $\alpha = 0.05/8 = 0.006$).

To investigate differences in the mean volumes and FA of FAT bilaterally, two-way ANOVAs were employed with Group (AD vs. HS) as between-subjects factor and Side (Right vs. Left) as within-subjects factor.

When considering the mean FA of FAT bilateral volumes of FAT were entered as covariates of no interest. Correlations between mean FA of bilateral FAT and age,

education, and MMSE score were calculated using Pearson's coefficient in patients and controls respectively. Bonferroni's correction was applied (p value threshold for significance was computed as $\alpha = 0.05/3 = 0.01$). Lastly, associations between mean FA of bilateral FAT and the cognitive measures were tested in AD and HS. Bonferroni's correction was applied (p value threshold for significance was computed as $\alpha = 0.05/8 = 0.006$).

In voxel-wise analyses, between-group differences and correlations with cognitive tests were accepted as significant at p values < 0.05 FWE-cluster level corrected (clusters formed at $p < 0.001$, uncorrected).

RESULTS

Demographical characteristics of participants

As reported in Table 1, there were no significant differences between groups in mean age ($F_{1,46} = 2.74$, $p = 0.10$) and in years of formal education ($F_{1,46} = 2.16$, $p = 0.15$).

Conversely, there was a statistically significant difference in gender distribution (Chi-square = 6,76, $df = 1$, $p = 0.009$). As a consequence, gender was entered as an additional covariate of no interest in all the performed analyses (both for behavioral and imaging data). As expected, compared to HS, patients reported significantly worse scores on the MMSE ($F_{1,46} = 102.1$, $p < 0.001$). Moreover, patients with AD showed higher MTA scale scores compared to HS ($F_{1,46} = 127.6$, $p < 0.001$).

Neuropsychological assessment

From a clinical viewpoint, AD patients exhibited normal levels of comprehension, spontaneous speech, and their fluency was characterized by anomia but not by agrammatism. As expected, there was no evidence of language disabilities in HS.

As shown in Table 2, AD patients compared to HS reported significantly worse mean scores on each administered cognitive tests, with the exception of the Copy of Drawings with landmarks and the Naming test. However, when considering individual performance, 11 out of 23 (47.8%) AD patients reported scores below the normality cut-off on the Copy of Drawings with landmarks.

FAT tractography

Bilateral FAT was successfully reconstructed in all participants.

When considering the volumes of the FAT no significant main effect of Group ($F_{1,46} = 0.679$, $p = 0.414$; mean AD = 6300; mean HS = 6678), of Side ($F_{1,46} = 2.69$, $p = 0.107$; Left = 6299, Right = 6678) or interaction Group by Side ($F_{1,46} = 0.614$, $p = 0.437$) were detected.

When considering the mean FA of FAT no main effect of Group ($F_{1,43} = 0.184$, $p = 0.669$; mean AD = 0.337; mean HS = 0.341) or Side ($F_{1,46} = 1.426$, $p = 0.238$; mean Left side = 0.338; mean Right side: 0.340) emerged. Interestingly, a significant Group by Side interaction ($F_{1,46} = 8.584$, $p = 0.005$) (Figure 2) was found. As shown by planned comparisons, this interaction was due to a significant reduction ($F_{1,46} = 8.164$, $p = 0.006$) in the mean FA of the left (mean = 0.331) compared to the right side FAT (mean = 0.342) in AD patients. In HS, no differences emerged ($F_{1,46} = 1.571$, $p = 0.216$) between the left (mean = 0.344) compared to right side FAT (mean = 0.339).

Insert Figure 2 around here

No significant associations emerged between FAT and demographic (age and education), and clinical (MMSE scores) characteristics in AD patients or in controls. Conversely, when we considered the association with cognitive profile we found significant positive correlations between the mean FA of right FAT and tests assessing

constructional praxis (Figure 3), Copy of drawings ($r = 0.76$, $p = 0.007$) and Copy of drawings with landmarks ($r = 0.57$, $p = 0.004$) in AD patients but not in controls ($r = -0.68$, $p = 0.06$, and $r = -0.08$, $p = 0.85$, respectively).

Insert Figure 3 around here

Voxel-wise analyses of FAT

Compared to HS, patients with AD showed a significant reduction in the FA of bilateral FAT, mainly in the SMA (BA6) and in the pars opercularis of the inferior frontal gyrus (BA44) (Figure 4).

Insert Figure 4 around here

A significant positive correlation between the FA of FAT and cognitive measures was also found in AD patients (see Figure 5). In particular, we observed a significant correlation between 1) the FAT and tests assessing constructional praxis (bilaterally with the Copy of drawings with Landmarks, and in the left hemisphere with Copy of drawings), and 2) the right FAT and test assessing visuo-spatial logical reasoning (Raven's Coloured Progressive Matrices). No other significant correlations were detected.

Insert Figure 5 around here

DISCUSSION

The aim of the present study was to assess the role played by FAT, an associative bundle involved in language's processes as spontaneous speech, speech fluency and speech initiation [15, 37] in AD pathophysiology. The role of FAT has been previously investigated in patients showing languages disorders due to different conditions, such as neurodegenerative disorders (e.g. primary progressive aphasia) [14] or focal brain lesions (e.g. brain tumors). We explored here the potential contribution of FAT damage

to constructional praxis and other cognitive disabilities in AD, based on the knowledge that the areas connected by the FAT, namely Broca's area, ACC, SMA and pre-SMA are involved in movement initialization and motor organization. To this aim, we recruited a group of patients with a probable diagnosis of typical AD, with a clinical onset characterized by predominant memory deficits. As expected, from a neuropsychological viewpoint AD patients showed a widespread cognitive impairment that did not involve language abilities. From a neuroimaging perspective, we found a significant reduction of FA in FAT both when considering the mean tract FA, a global measure of WM damage, and when using a voxel by voxel approach. Specifically, we found a significant Group by Side interaction due to the reduction of mean FA on the left compared to the right FAT in AD patients. This is in contrast with previous observations of FAT being thicker in the left hemisphere of right-handed individuals [15], consistently with its association with languages processes [12, 18, 37]. It is remarkable that the observed microstructural damages were, likely, independent from a partial-volume effect. Indeed, we did not find any significant difference in the volumes of the tracts. In our opinion this finding support the hypothesis that FAT abnormalities were not due to merely atrophic changes, but more likely due to specific WM alterations.

Compared to controls, in AD patients the voxel-wise analysis revealed a significant reduction of FA in the pars opercularis of the interior frontal gyrus, mainly in the left hemisphere. Interestingly, significant correlations were found between these FAT microscopic abnormalities and patients' cognitive measures. In particular, the mean FA of the right FAT was associated with scores on both tests assessing constructional praxis (i.e., Copy of drawings and Copy of drawings with landmarks tests).

Additionally, the voxel-wise analysis confirmed and extended the correlation between FAT's damage and patients' cognitive deficits, revealing associations not only with

constructional praxis but also with visuo-spatial logical reasoning (i.e., Raven's Coloured Matrices).

As previously reported [38], constructional apraxia is defined as an acquired deficit of the ability to reproduce spatial relations, in the absence of motor impairments.

Typically, patients with constructional apraxia perform poorly on drawing tasks or when arranging blocks or objects. Existing literature suggests that constructional apraxia is a complex disorder due to impairment of either basic abilities, such as visuo-spatial perception and analysis, visuo-motor integration, motor skills [39], or executive functions, such as planning and monitoring responses [40]. It appears that constructional apraxia requires the integrity of a large and complex cognitive network. A disruption of this network at any level may result in a variety of praxis disturbances [41]. Such deficits are typically observed in patients with focal brain lesions [39], but they can also be present in patients with neurodegenerative conditions, such as AD [24, 25, 42, 43] or frontotemporal dementia [23]. Despite its precise anatomical-functional localization being still under debate [24, 25, 41, 44, 45], constructional apraxia is generally observed in patients with parietal [39] or frontal lobe [23] damages. For example, in a previous volumetric study we found grey matter atrophy restricted in the parietal, occipital and temporal brain areas of patients with AD and evidence of constructional apraxia [4]. The present study suggested a direct involvement of the FAT in different aspects of constructional apraxia abilities as measured by Copy of drawings tasks and by Raven's Coloured Matrices. In particular, the FAT, connecting the SMA, the pre-SMA, and the ACC with the pars opercularis of the Broca's area [12] is considered as part of a "motor stream" [19] involved in the speech programming in terms of cognitive control to response selection, initiation, sequencing [19], and coordination [12]. The pre-SMA and ACC have been considered as critically involved in movement initialization (i.e., the process of identification/selection of motor

responses) [21, 22], whereas more lateral areas such as the BA6 and the Broca's area (BA44) have been considered involved in movement organization. In particular, Broca's area is crucial for the syntactic discourse that depends on word order. Broca's area is critical in identifying the sequential order of word placement [46]. In an analogous motor role, Broca's area might be involved in the order selection for organized movement [47] in praxis abilities. Disconnection between these areas (SMA, pre-SMA and Broca's area) due to FAT damages might therefore produce not only language, but also non-language deficits, such as apraxia. Indeed, damages of this bundle have been previously associated with various degrees of speech impairment, from total inability to initiate speech (i.e., mutism) to mild altered fluency [48]. The microstructural damage of FAT was also previously found associated with verbal fluency deficits, mainly in patients with the agrammatic-variant of PPA [14]. In this variant of PPA, patients show several languages' deficits including the "apraxia of speech" [49], a deficit in which the motor engrams needed to produce verbal speech are lost in the absence of motor impairments. We hypothesize that the FAT might also be involved in the planning of the motor engrams needed to execute the grapho-motor movements necessary to produce a drawing, and that the praxis deficits observed in AD are therefore in line with what has been observed in agrammatic-PPA patients. This hypothesis is supported by the strong anatomical association between FAT and the frontal-striatal tract (FST) [16], a bundle connecting the SMA and pre-SMA with caudate nucleus [50] and involved in motor control, including manual coordination [16]. In its rostral part (around pre-SMA) the FAT is intermingling and overlapping with FST [16], whereas, caudally, FAT is running in a little more anterolateral side than FST [16]. Moreover, the present findings are supported by recent evidence of the role played by FAT in the visually guided hand movements [51], necessary to perform the grapho-motor task underlying the drawing tests.

In conclusion, this study contributes in clarifying some novel pathophysiological aspects underlying constructional apraxia in AD. The pattern of structural disconnection that we identified here, and its associations with patients' performance in praxis tests, might inform future neuropsychological approaches to define a more complex spectrum of apraxia, which might differ at different transitional stages of typical AD. Future longitudinal studies are needed to confirm and extend our current findings.

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Conflict of interests

None of the Authors has any conflict of interest to disclose

REFERENCES

- [1] Winblad B, Amouyel P, Andrieu S, Ballard C, Brayne C, Brodaty H, Cedazo-Minguez A, Dubois B, Edvardsson D, Feldman H, Fratiglioni L, Frisoni GB, Gauthier S, Georges J, Graff C, Iqbal K, Jessen F, Johansson G, Jönsson L, Kivipelto M, Knapp M, Mangialasche F, Melis R, Nordberg A, Rikkert MO, Qiu C, Sakmar TP, Scheltens P, Schneider LS, Sperling R, Tjernberg LO, Waldemar G, Wimo A, Zetterberg H (2016) Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol* **15**, 455-532.
- [2] Bozzali M, Padovani A, Caltagirone C, Borroni B (2011) Regional grey matter loss and brain disconnection across Alzheimer disease evolution. *Curr Med Chem* **18**, 2452-2458.
- [3] Delbeuck X, Collette F, Van der Linden M. Is Alzheimer's disease a disconnection syndrome? (2007) Evidence from a crossmodal audio-visual illusory experiment. *Neuropsychologia* **45**, 3315-3323.
- [4] Serra L, Cercignani M, Lenzi D, Perri R, Fadda L, Caltagirone C, Macaluso E, Bozzali M (2010) Grey and White Matter Changes at Different Stages of Alzheimer's Disease. *J Alzheimers Dis* **19**, 147-159.
- [5] Lee SH, Coutu JP, Wilkens P, Yendiki A, Rosas HD, Salat DH (2015) Tract-based analysis of white matter degeneration in Alzheimer's disease. *Neuroscience* **301**, 79-89.
- [6] Serra L, Cercignani M, Basile B, Spano B, Perri B, Fadda L, Marra C, Giubilei F, Caltagirone C, Bozzali M (2012) White Matter Damage Along the Uncinate Fasciculus Contributes to Cognitive Decline in AD and DLB. *Curr Alzheimer Res* **9**, 326-333.
- [7] Bozzali M, Giulietti G, Basile B, Serra L, Spanò B, Perri R, Giubilei F, Marra C, Caltagirone C, Cercignani M (2012) Damage to the cingulum contributes to Alzheimer's disease pathophysiology by deafferentation mechanism. *Hum Brain Mapp* **33**, 1295-1308.

- [8] Agosta F, Pievani M, Sala S, Geroldi C, Galluzzi S, Frisoni GB, Filippi M (2011) White matter damage in Alzheimer disease and its relationship to gray matter atrophy. *Radiology* **258**, 853-863.
- [9] Migliaccio R, Agosta F, Possin KL, Rabinovici GD, Miller BL, Gorno-Tempini ML (2012) White matter atrophy in Alzheimer's disease variants. *Alzheimers Dement* **8**, 78-87.
- [10] Franssen EH, Kluger A, Torossian CL, Reisberg B (1993) The neurologic syndrome of severe Alzheimer's disease. Relationship to functional decline. *Arch Neurol* **50**, 1029-1039.
- [11] Meng JZ, Guo LW, Cheng H, Chen YJ, Fang L, Qi M, Jia ZY, Mohammed W, Hong XN (2012) Correlation between cognitive function and the association fibers in patients with Alzheimer's disease using diffusion tensor imaging. *J Clin Neurosci* **19**, 1659-1663.
- [12] Catani M, Dell'acqua F, Vergani F, Malik F, Hodge H, Roy P, Valabregue R, Thiebaut de Schotten M (2012) Short frontal lobe connections of the human brain. *Cortex* **48**, 273-291.
- [13] Broce I, Bernal B, Altman N, Tremblay P, Dick AS (2015) Fiber tracking of the frontal aslant tract and subcomponents of the arcuate fasciculus in 5-8-year-olds: Relation to speech and language function. *Brain Lang* **149**, 66-76.
- [14] Catani M, Mesulam MM, Jakobsen E, Malik F, Martersteck A, Wieneke C, Thompson CK, Thiebaut de Schotten M, Dell'Acqua F, Weintraub S, Rogalski E (2013) A novel frontal pathway underlies verbal fluency in primary progressive aphasia. *Brain* **136**, 2619-2628.
- [15] Fujii M, Maesawa S, Motomura K, Futamura M, Hayashi Y, Koba I, Wakabayashi T (2015) Intraoperative subcortical mapping of a language-associated deep frontal tract

connecting the superior frontal gyrus to Broca's area in the dominant hemisphere of patients with glioma. *J Neurosurg* **122**, 1390-1396.

[16] Kinoshita M, de Champfleury NM, Deverdun J, Moritz-Gasser S, Herbet G, Duffau H (2015) Role of fronto-striatal tract and frontal aslant tract in movement and speech: an axonal mapping study. *Brain Struct Funct* **220**, 3399-3412.

[17] Sierpowska J, Gabarrós A, Fernandez-Coello A, Camins À, Castañer S, Juncadella M, de Diego-Balaguer R, Rodríguez-Fornells A (2015) Morphological derivation overflow as a result of disruption of the left frontal aslant white matter tract. *Brain Lang* **142**, 54-64.

[18] Basilakos A, Fillmore PT, Rorden C, Guo D, Bonilha L, Fridriksson J (2014) Regional white matter damage predicts speech fluency in chronic post-stroke aphasia. *Front Hum Neurosci* **8**, 1-9.

[19] Dick AS, Bernal B, Tremblay P (2014). The language connectome: new pathways, new concepts. *Neuroscientist* **20**, 453-467.

[20] Hickok G, Poeppel D (2007) The cortical organization of speech processing. *Nat Rev Neurosci* **8**, 393-402.

[21] Hoffstaedter F, Grefkes C, Caspers S, Roski C, Palomero-Gallagher N, Laird AR, Fox PT, Eickhoff SB (2014) The role of anterior midcingulate cortex in cognitive motor control: evidence from functional connectivity analyses. *Hum Brain Mapp* **35**, 2741-2753.

[22] Nachev P, Wydell H, O'Neill K, Husain M, Kennard C (2007) The role of the pre-supplementary motor area in the control of action. *Neuroimage* **36**, 155-163.

[23] Grossi D, Fragassi NA, Chiacchio L, Valoroso L, Tuccillo R, Perrotta C, Rapone P, Conchiglia G, Trojano L (2002) Do visuospatial and constructional disturbances differentiate frontal variant of frontotemporal dementia and Alzheimer's disease? An experimental study of a clinical belief. *Int J Geriatr Psychiatry* **17**, 641-648.

- [24] Serra L, Fadda L, Perri R, Caltagirone C, Carlesimo GA (2009) The closing-in phenomenon in the drawing performance of Alzheimer's disease patients: a compensation account. *Cortex* **46**, 1031-1036.
- [25] Serra L, Fadda L, Perri R, Spanò B, Marra C, Castelli D, Torso M, Makovac E, Cercignani M, Caltagirone C, Bozzali M (2014) Constructional apraxia as a distinctive cognitive and structural brain feature of pre-senile Alzheimer's disease. *J Alzheimers Dis.* **38**, 391-402.
- [26] McKhann GM, Knopman DS, Chertkow H, Hymanf BT , Jack CR Jr.,Kawash CH, Klunk WE , Koroshetz WJ, Manlym JJ, Mayeuxm R, Mohs RC, Morris JC, Rossor MN , Scheltens P, Carrillo MC, Thies B , Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.
- [27] American Psychiatric Association (APA) (2013) DSM-V Diagnostic and Statistical Manual of Mental Disorders. Milano: Edizione Italiana: Masson.
- [28] Scheltens P, Launer LJ, Barkhof F, Weinstein HC, van Gool WA (1995) Visual assessment of medial temporal lobe atrophy on magnetic resonance imaging: interobserver reliability. *J. Neurol* **242**, 557-560.
- [29] Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* **12**, 189-198.
- [30] Magni E, Binetti G, Padovani A, Cappa SF, Bianchetti A, Trabucchi M (1996) The Mini-Mental State Examination in Alzheimer's disease and multi-infarct dementia. *Int Psychogeriatr* **8**, 127-134.

- [31] Hachinski VC, Iliff LD, Zilhka E, Du Boulay GH, McAllister VL, Marshall J, Ross Russell RW, Symon L (1975) Cerebral blood flow in dementia. *Arch Neurol* **32**, 632-637.
- [32] Carlesimo GA, Caltagirone C, Gainotti G (1996) The Mental Deterioration Battery: normative data, diagnostic reliability and qualitative analyses of cognitive impairment. The Group for the Standardization of the Mental Deterioration Battery. *Eur Neurol* **36**, 378-384.
- [33] Monaco M, Costa A, Caltagirone C, Carlesimo GA (2013) Forward and backward span for verbal and visuo-spatial data: standardization and normative data from an Italian adult population. *Neurol Sci* **34**, 749-754.
- [34] Miceli G, Laudanna A, Burani C, Capasso R (1991) Batteria per l'analisi dei deficit afasici. Associazione per lo sviluppo delle ricerche neuropsicologiche. Milano: Berdata.
- [35] Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* **23**, 208-219.
- [36] Parker GJ, Haroon HA, Wheeler-Kingshott CA (2003) A framework for a streamline-based probabilistic index of connectivity (PICO) using a structural interpretation of MRI diffusion measurements. *J Magn Reson Imaging* **18**, 242-254.
- [37] Kinoshita M, Shinohara H, Hori O, Ozaki N, Ueda F, Nakada M, Hamada J, Hayashi Y (2012) Association fibers connecting the Broca center and the lateral superior frontal gyrus: a microsurgical and tractographic anatomy. *J Neurosurg* **116**, 323-330.
- [38] Kleist K (1934) *Konstruktive (optische) Apraxie*. Barth ed. Leipzig.

- [39] Villa G, Gainotti G, De Bonis C (1986) Constructive disabilities in focal brain-damaged patients. Influence of hemispheric side, locus of lesion and coexistent mental deterioration. *Neuropsychologia* **24**, 497-510.
- [40] Warrington EK, James M, Kinsbourne M (1966) Drawing disability in relation to laterality of cerebral lesion. *Brain* **89**, 53-82.
- [41] Smith AD, Gilchrist ID (2005) Within-object and between-object coding deficits in drawing production. *Cogn Neuropsychol* **22**, 523-537.
- [42] Della Sala S, Spinnler H, Trivelli C (1996) Slowly progressive impairment of spatial exploration and visual perception. *Neurocase* **2**, 299-323.
- [43] Smith MZ, Esiri MM, Barnetson L, King E, Nagy Z (2001) Constructional apraxia in Alzheimer's disease: association with occipital lobe pathology and accelerated cognitive decline. *Dement Geriatr Cogn Disord* **12**, 281-288.
- [44] Trojano L, Fragassi NA, Chiacchio L, Izzo O, Izzo G, Di Cesare G, Cristinzio C, Grossi D (2004) Relationships between constructional and visuospatial abilities in normal subjects and in focal brain-damaged patients. *J Clin Exp Neuropsychol* **26**, 1103-1112.
- [45] Trojano L, Grossi D, Flash T (2009) Cognitive neuroscience of drawing: contributions of neuropsychological, experimental and neurofunctional studies. *Cortex* **45**, 269-277.
- [46] Grodzinsky Y, Friederici AD (2006) Neuroimaging of syntax and syntactic processing. *Curr Opin Neurobiol* **16**, 240-246.
- [47] Clerget E, Badets A, Duqué J, Olivier E (2011) Role of Broca's area in motor sequence programming: a cTBS study. *Neuroreport* **22**, 965-969.
- [48] Ackermann H, Riecker A (2010) The contribution(s) of the insula to speech production: a review of the clinical and functional imaging literature. *Brain Struct Funct* **214**, 419-433.

- [49] Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, Cappa SF, Ogar JM, Rohrer JD, Black S, Boeve BF, Manes F, Dronkers NF, Vandenberghe R, Rascovsky K, Patterson K, Miller BL, Knopman DS, Hodges JR, Mesulam MM, Grossman M (2011) Classification of primary progressive aphasia and its variants. *Neurology* **76**, 1006-1014.
- [50] Lehericy S, Ducros M, Krainik A, Francois C, Van de Moortele PF, Ugurbil K, Kim DS (2004) 3-D diffusion tensor axonal tracking shows distinct SMA and pre-SMA projections to the human striatum. *Cereb Cortex* **14**, 1302-1309.
- [51] Budisavljevic S, Dell'Acqua F, Djordjilovic V, Miotto D, Motta R, Castiello U (2017) The role of the frontal aslant tract and premotor connections in visually guided hand movements. *Neuroimage* **146**, 419-428.

Figures Legend

Figure 1. Seed and waypoints used to reconstruct bilaterally the FAT

The figure illustrates the anatomical points (in red) used as seed and waypoints to reconstruct the FAT bilaterally. Seed and waypoints were manually drawn on each individual FA's map. For the purpose of the illustration the anatomical seed and waypoints are overlaid onto the FMRIB_FA template using FSL (<http://fsl.fmrib.ox.ac.uk/>).

Abbreviations: FAT= Frontal aslant tract; R = right.

Figure 2. Mean FA of bilateral FAT in AD patients and healthy controls.

The graph illustrates the mean FA in the FAT bilaterally in patients and healthy controls. AD patients showed a significant reduction (highlighted with the asterisk) in the mean FAT of the left (in green) compared to the right hemisphere (in blue). No significant leftward reduction (or vice versa) was found in the FAT of healthy controls.

Abbreviations: AD = Alzheimer's disease; HS = Healthy subjects; FAT= Frontal aslant tract; L = left; R = right.

Figure 3. Plot of correlations between mean FA of right FAT and tests assessing constructional praxis in patients with AD and in healthy subjects.

Significant correlations between the mean FA of the right FAT and performances scores on test assessing constructional praxis (Copy of drawings in Panel A; and Copy of drawings with landmarks in Panel B) were found in AD patients (in red) but not in healthy controls (in blue).

Abbreviations: AD = Alzheimer's disease; HS = Healthy subjects; FA = Fractional anisotropy; FAT = Frontal aslant tract.

Figure 4. Voxel-wise analysis on FAT in patients with AD and healthy subjects.

The figure illustrates the between-group comparison (in red) in the FA of bilateral FAT (in blue) voxel-by-voxel. A significant FA reduction, mainly in the SMA and in the pars opercularis of the inferior frontal gyrus bilaterally was found in AD patients compared to HS. The results are FWE-corrected at cluster level ($p < 0.05$) and overlaid onto a FMRIB_FA template using FSL (<http://fsl.fmrib.ox.ac.uk/>)

Abbreviations: AD = Alzheimer's disease; HS = Healthy subjects; FA = Fractional anisotropy; FAT = Frontal aslant tract; SMA= Supplementary motor area; L = left; R = right.

Figure 5. Correlation analyses between FA of FAT bilaterally and cognitive measures in AD patients.

Significant voxel-by-voxel positive correlations between FA of FAT (in blue) and cognitive measures were found in AD patients. Specifically, FAT correlated bilaterally with the Copy of drawings with landmark (in red), with the Copy of drawings (in yellow) in the left side, and with the Raven's Coloured Progressive Matrices (in green) in the right side. The results are FWE-corrected at cluster level ($p < 0.05$) and overlaid onto a FMRIB_FA template using FSL (<http://fsl.fmrib.ox.ac.uk/>).

Abbreviations: AD = Alzheimer's disease; FAT = Frontal aslant tract; R = right; CDELP = Copy of drawings with landmark; CD = Copy of drawings; RCPM = Raven's Coloured Progressive Matrices.

Table 1. Principal demographic and clinical characteristics of studied subjects.

	AD n=23	HS n=25
Mean (SD) age [years]	71.2 (8.2)	67.6 (6.9)
Gender (M/F)	7/16*	17/8
Mean (SD) years of formal education	10.8 (4.1)	12.3 (3.1)
Mean (SD) MMSE score	17.6 (4.4)*	28.7 (1.7)
Mean (SD) MTA	3.0 (0.8) *	0.5 (0.5)

* AD vs HS $p < 0.05$

Abbreviations: HS = healthy subjects; AD = Alzheimer disease; MMSE = Mini Mental State Examination; MTA= medial temporal lobe scale.

Table 2. Performance of AD and HS groups on neuropsychological tests.

Domain	Test	AD	HS
Verbal episodic long-term memory			
	15-Rey's words List:		
	Immediate recall (cut-off ≥ 28.5)	4.2 (4.7)*	16.2 (7.0)
	Delayed recall (cut-off ≥ 4.6)	1.6 (1.8)*	9.7 (2.2)
Verbal working memory			
	Digit span backward	2.0 (1.4)*	4.1 (0.7)
Executive functions			
	Phonological Word Fluency (cut-off ≥ 17.3)	10.4 (4.7)*	37.9 (9.0)
Language			
	Naming of objects (cut-off ≥ 22)	21.6 (7.7)	29.0 (0.8)
Reasoning			
	Raven's Coloured Progressive Matrices (cut-off ≥ 18.9)	19.8 (6.4)*	30.9 (4.3)
Constructional praxis			
	Copy of drawings (cut-off ≥ 7.1)	6.6 (3.6)*	10.8 (1.2)
	Copy of drawings with landmarks (cut-off ≥ 61.8)	54.3 (20.9)	69.5 (0.5)

* AD vs HS $p < 0.006$ Bonferroni corrected.

Abbreviations: AD = Alzheimer's disease; HS = Healthy Subjects.

Figure 1

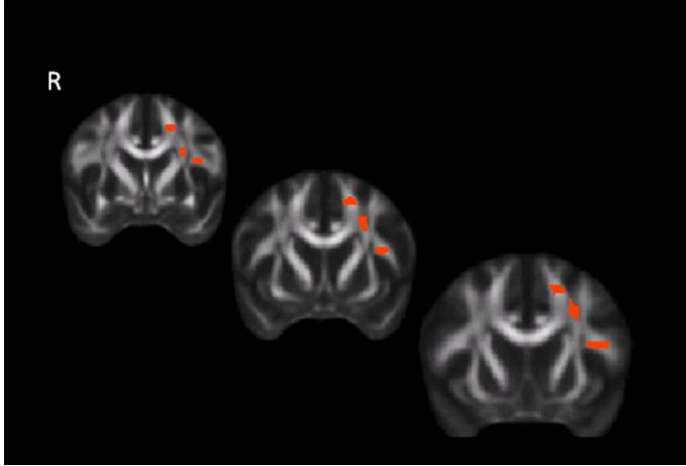


Figure 2.

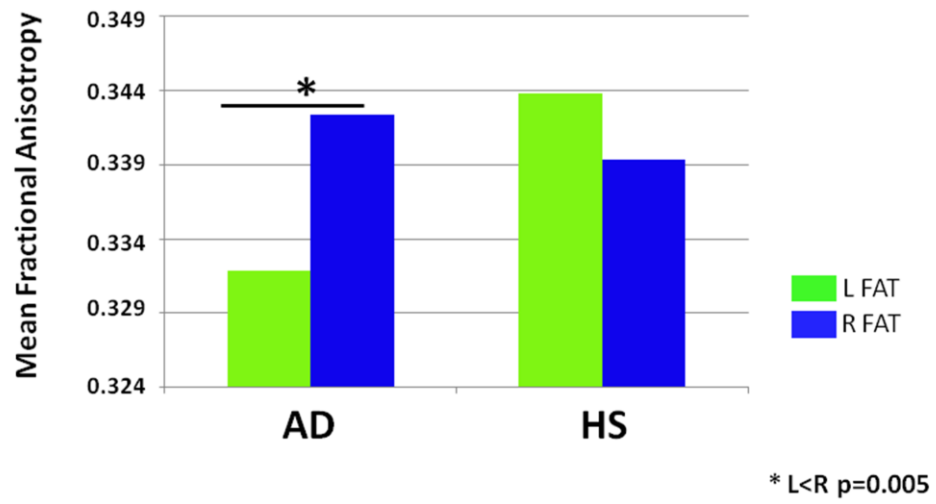
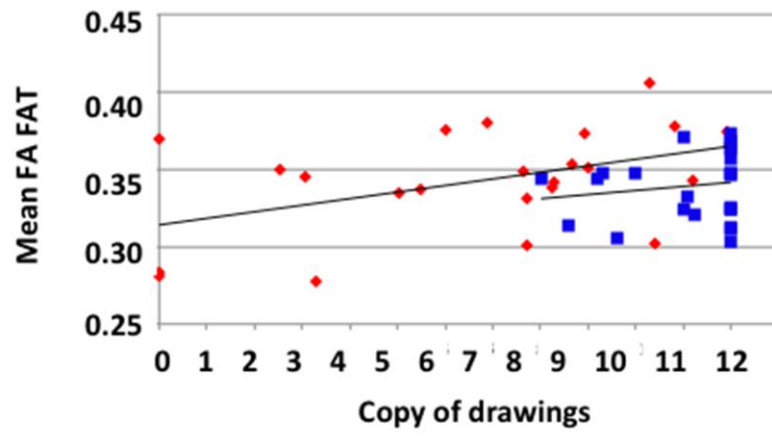
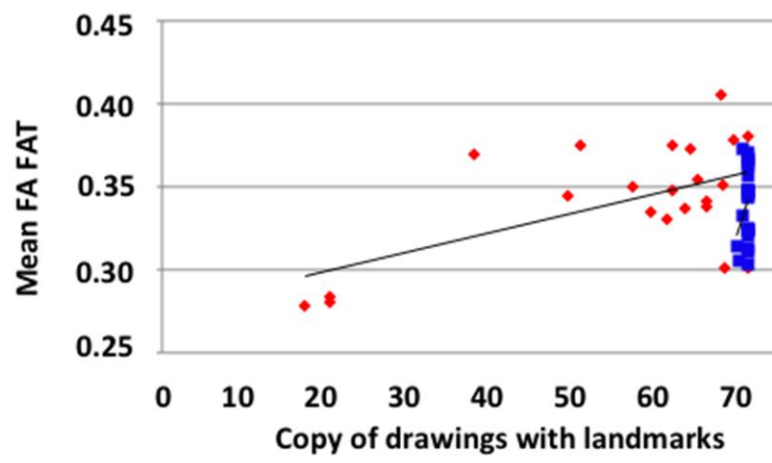


Figure 3.

A



B



◆ AD
■ HS

Figure 4.

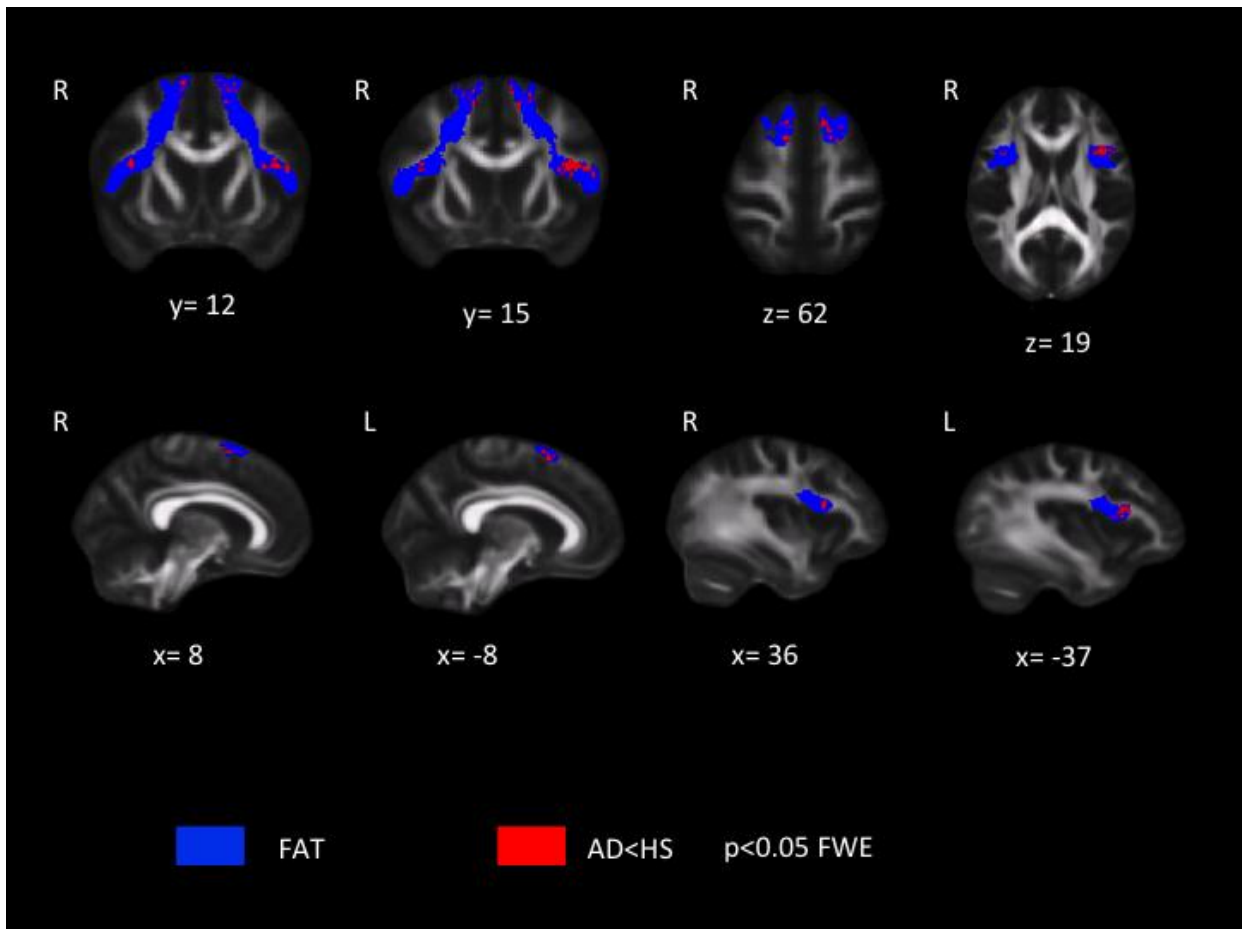


Figure 5.

