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Mapping whole brain connectivity changes: The potential impact of different surgical resection approaches for temporal lobe epilepsy

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ABSTRACT

In neurosurgery there are several situations that require transgression of the temporal cortex. For example, a subset of patients with temporal lobe epilepsy require surgical resection (most typically, en-bloc anterior temporal lobectomy). This procedure is the gold standard to alleviate seizures but is associated with chronic cognitive deficits. In recent years there have been multiple attempts to find the optimum balance between minimising the size of resection in order to preserve cognitive function, while still ensuring seizure freedom. Some attempts involve reducing the distance that the resection stretches back from the temporal pole, whilst others try to preserve one or more of the temporal gyri. More recent advanced surgical techniques (selective amygdalo-hippocamptectomies) try to remove the least amount of tissue by going under (sub-temporal), over (trans-Sylvian) or through the temporal lobe (middle-temporal), which have been related to better cognitive outcomes. Previous comparisons of these surgical techniques focus on comparing seizure freedom or behaviour post-surgery, however there have been no systematic studies showing the effect of surgery on white matter connectivity. The main aim of this study, therefore, was to perform systematic 'pseudo-neurosurgery' based on existing resection methods on healthy neuroimaging data and measuring the effect on long-range connectivity. We use anatomical connectivity maps (ACM) to determine long-range disconnection, which is complementary to existing measures of local integrity such as fractional anisotropy or mean diffusivity. ACMs were generated for each diffusion scan in order to compare whole-brain connectivity with an 'ideal resection', nine anterior temporal lobectomy and

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three selective approaches. For en-bloc resections, as distance from the temporal pole increased, reduction in connectivity was evident within the arcuate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and the uncinate fasciculus. Increasing the height of resections dorsally reduced connectivity within the uncinate fasciculus. Sub-temporal amygdalohippocampectomy resections were associated with connectivity patterns most similar to the 'ideal' baseline resection, compared to trans-Sylvian and middle-temporal approaches. In conclusion, we showed the utility of ACM in assessing long-range disconnections/disruptions during temporal lobe resections, where we identified the sub-temporal resection as the least disruptive to long-range connectivity which may explain its better cognitive outcome. These results have a direct impact on understanding the amount and/or type of cognitive deficit post-surgery, which may not be obtainable using local measures of white matter integrity.

1. Introduction

In neurosurgery there are several situations that require transgression of the temporal cortex, most notably for access to the temporal horn, temporal tumours or medial temporal structures. This study focussed on the latter as an important clinical exemplar and test-case for exploring the effect of different neurosurgical approaches on long-range white-matter connectivity. Temporal lobe epilepsy is a chronic disorder that is characterised by recurrent, unprovoked focal seizures typically originating within the temporal lobe, specifically in the hippocampus and surrounding mesial tissue. Often seizures are controlled with anti-epileptic drugs (AEDs) however sometimes medication is not an effective method to alleviate seizures. If anti-epileptic drugs fail to control these focal seizures, surgical resection may be necessary.

Most commonly, the surgical aim in temporal lobe epilepsy is to resect the hippocampus and surrounding tissue (i.e., the amygdala), however the best surgical method to approach these mesial structures is unclear. Ideally, one would want to access the structures with minimum amount of damage to the surrounding tissue, however the mesial location and network of blood vessels makes this a challenge. Historically complete or partial unilateral resection of the temporal lobe (en-bloc anterior temporal lobectomies) were the most common surgical method and are still considered the gold standard technique to alleviate seizures (Chang, Englot, & Vadera, 2015; Jack, Sharbrough, & Marsh, 1988) Typically en-bloc lobectomies involve surgically resecting between 4 and 6 cm back from the temporal pole (depending on whether it is the dominant hemisphere) and resections include all three temporal gyri; inferior temporal gyrus (ITG), middle temporal gyrus (MTG) and superior temporal gyrus (STG) (Wiebe, Blume, Girvin, & Eliasziw, 2001). These methods have, however, been associated with cognitive deficits in episodic memory, language and semantic memory over-and-above pre-surgical behavioural problems related to the epilepsy (Giovagnoli et al., 2016).

Despite the association between en-bloc resections and increased seizure freedom, many surgeons have differing opinions over the optimal resection volume to preserve cognitive functions. Larger resections have been associated with increased chance of seizure freedom, however removing unnecessary tissue raises concerns regarding poor behavioural outcomes post-surgery (Helmstaedter, 2013). There can also be a discrepancy between planned resection size and actual resection size. This may be due to a number of factors, but predominantly the deformation of the brain, typically shrinkage, when the skull is opened (Hartkens et al., 2003) which may result in a slightly larger resection than planned. In recent years there have been multiple attempts to find the optimum balance between minimising the size of resection in order to preserve cognitive function, while still ensuring seizure freedom. Attempts have involved reducing the length of the resection from the temporal pole, whilst others try to preserve one or more of the temporal gyri (Gross, Mahmoudi, & Riley, 2015; Wiebe et al., 2001).

More recent advanced surgical techniques try to limit deficits through selective amygdalo-hippocamptectomies. These, often complex, surgeries attempt to minimise the amount of tissue resected in order to gain access to the mesial structures (Gross et al., 2015). Examples of these surgical techniques include gaining access under the temporal lobe (sub-temporal), over the temporal lobe (trans-Sylvian) or through the temporal lobe (middle temporal) (Helmstaedter, 2013). The sub-temporal approach involves the removal of the fusiform gyrus in order to gain access to the temporal horn which allows resection of the mesial structures. This selective method is thought to be the least invasive surgical method as it preserves the optic radiation and the language areas (Yang et al., 2009). The disadvantages of this surgical method are that there have to be large retractions of the brain and there is a high risk of injury to the vein of Labbé, making this technique very technically complex (Yang et al., 2016). The trans-Sylvian approach accesses the mesial structures through the Sylvian fissure and bores into the temporal stem. This allows access to the hippocampus and surrounding regions while maximising preservation of the temporal lobe, although risks injuring the anterior circulation vasculature and therefore is rarely carried out (Kovanda, Tubbs, & Cohen-Gadol, 2014). The transcortical (or middle-temporal) approach is technically simpler as it poses less risk to lacerating a vein than other selective methods. Access to the mesial structures is gained by resecting through the middle temporal gyrus.

There have been several attempts to compare the more classical en-bloc approach to selective methods, with most of this research focused on either seizure freedom or neuropsychological outcomes post-surgery. Anterior temporal lobectomies have been shown to have an improved rate of seizure freedom compared to more selective approaches (Josephson et al., 2013). These results, however, do not appear to be consistent and other studies report no significant difference in seizure freedom between either surgical method (Hans Clusmann et al., 2002; Schramm, 2008). A recent meta-analysis regarding neuropsychological outcomes after different resection methods concluded that overall there were no differences between selective amydalo-hippocampectomies compared to en-bloc anterior temporal lobectomy (Taner Tanriverdi et al., 2010).

There are a number of potential confounds that might lead to such inconsistencies. First, there are individual differences in the amount of tissue that is resected within each surgical method, which could change the behavioural outcomes as much as the resection type. Secondly, all individuals who have a resection have had severe epilepsy for an extended period of time, which is likely to affect behaviour pre-surgically. Thirdly, each individual only receives one form of surgery, so despite best efforts to match individuals, an accurate direct comparison is not possible. These, along with other confounds, are likely to explain the inconsistencies across studies investigating the effect of different surgical methods. Recently, there has been growing interest in incorporating diffusion tensor imaging (DTI) in the surgical management of temporal lobe epilepsy surgery (Sivakanthan, Neal, Murtagh, & Vale, 2016). A recent study assessed the preoperative integrity of white matter tracts associated with the generation and propagation of seizures within the temporal lobe in an attempt to understand why some patients still suffered seizures post-surgery (Keller et al., 2017). The reconstructed tracts included the uncinate fasciculus, the fornix and parahippocampal white matter bundles, and the calculated local diffusion metrics included fractional anisotropy (FA) and mean diffusivity (MD). Seizure free patients had a larger extent of the uncinate fasciculus resected, suggesting that a smaller resection of the uncinate may not disconnect the anterior temporal epileptogenic network. In addition, only patients who still suffered post-surgical seizures we found to have diffusion metrics within the ipsilateral fornix which were significantly different to controls, suggesting that damage to the ipsilateral fornix may be associated with continued post-surgical seizures. Such studies highlight the importance of focussing on the connectivity pre- and post-surgery rather than solely the section of cortex resected. So far, DTI methods have focused on predicting seizure freedom and investigating local differences in white matter tracts, and few, if any, have concentrated on long-range white matter disconnection.

FA and MD are easy to quantify and have been shown to provide useful information about local white-matter integrity. For example, in Alzheimer's disease, a reduction of FA within the corpus callosum was found to correlate with scores on the Mini-Mental State Examination (Bozzali et al. (2002). In contrast, FA/MD cannot provide information about changes to long-range connectivity given that FA/MD values remain unchanged in remote regions (except over time where Wallerian degeneration may occur). Anatomical Connectivity Maps (ACM) were developed to identify long-range disconnection across the whole brain (Embleton, Morris, Haroon, Lambon Ralph, & Parker, 2007). This *long-range* connectivity measure provides a complementary alternative to *local integrity* metrics such as FA or MD. Using probabilistic fibre orientation estimates, ACMs are obtained by initiating streamlines from all parenchymal voxels. Each cumulative trajectory of the streamlines are saved across all voxels, which provide a final brain map that indicates how many times a streamline passed each voxel (i.e., global connectivity of each voxel (Bozzali et al., 2011). As noted in the example above, the local FA/MD measures would fail to identify changes outside the resected tissue, however long-range measures such as ACMs are able to detect connectivity changes as fewer streamlines would be identified at any voxel that was previously connected to the removed regions.

The main aim of this study was to investigate, systematically, how different temporal lobe resection strategies affect long-range disconnections to the whole brain. This was achieved by performing 'pseudo-neurosurgery' on high-resolution diffusion data from the Human Connectome Project (Fischl, 2012; Glasser et al., 2013; Jenkinson et al., 2002, 2012). Another benefit of this procedure is that we were able to perform 'pseudo-neurosurgery' multiple times on the same healthy participants in order to compare the outcomes of different pseudo-surgeries within the same participants.

Before exploring the effects of different neurosurgical approaches, we confirmed the validity of the ACM method for identifying long-range connectivity changes by focussing on the Papez circuit (Papez, 1937). This well-established neural circuit, associated with episodic memory function, encompasses various brain regions including the hippocampus and their associated long-range white-matter connections (Aggleton, 2008). Accordingly, if the ACM method is able to detect long-range disconnections then a pseudo-resection of the hippocampus should identify reduced connectivity to the remaining parts of the Papez circuit.

2. Materials and methods

2.1. *Human connectome data and preprocessing*

Forty structural pre-processed (Glasser et al., 2013; Jenkinson et al., 2002) and diffusion pre-processed (Andersson, Skare, & Ashburner, 2003; Andersson and Sotiropoulos, 2015, 2016) datasets were downloaded from the WU-Minn 1200 Human Connectome Project dataset release. Participants in this database were scanned on a customized Siemens 3T 'Connectome Skyra' using a standard 32-channel Siemens receive head coil and a 'body' transmission coil designed by Siemens specifically for the smaller space available using the special gradients of the WU-Minn and MGH-UCLA Connectome scanners. The scanner has a customised SC72 gradient insert and a customized body transmitter coil with 56 cm bore size (diffusion: Gmx = 100 mT/m, max slew rate = 91 mT/m/msec; readout/imaging: Gmax = 42 mT/m, max slew rate = 200 mT/

m/msec). The HCP Skyra has the standard set of Siemen's shim coils. To acquire the T1-weighted images, the 3D Magnetization Prepared Rapid Acquisition GRE (MP-RAGE) method was utilised with the following parameters; TR = 2400 msec, TE = 2.14 msec, TI = 1000 msec, flip angle = 8°, FOV = 224 × 224 mm, voxel size = .7 mm isotropic, BW = 210 Hz/Px and acquisition time = 7 min, 40 sec.

Diffusion-weighted scans were collected using an HCP-specific variant of a multiband diffusion sequence (Moeller et al., 2010), which applies simultaneous echo refocussing (SER) approach (Feinberg, Reese, & Wedeen, 2002; Reese, Benner, Wang, Feinberg, & Wedeen, 2009) to achieve multiplicative accelerations (Feinberg et al., 2010). Spin-echo EPI diffusion data acquisition used the following parameters: TE = 89.5 msec, TR = 5520 msec, 11 slices, 168 × 144 acquisition matrix, 210 × 180 FOV with 1.25 × 1.25 mm isotropic voxels.

Each diffusion session included six runs (each of approximately 10 min), representing three different gradient tables, with each table acquired once right-to-left and left-to-right phase encoding polarities, respectively. Each gradient table included roughly 90 diffusion weighting directions plus six b = 0 acquisitions interspersed throughout each run. Diffusion weighting consisted of three shells of b = 1000, b = 2000 and b = 3000 sec/mm^2. The diffusion directions were obtained using a toolbox available from the French Institute for Research in Computer Science and Automation (INRIA) which returns uniformly distributed directions in multiple q-space shells (Caruyer, Lenglet, Sapiro, & Deriche, 2013). The directions are optimised so that every subset of the first M directions is also isotropic. A vitamin E capsule was taped to the right temple of each subject to determine which was the right side of the image data.

The data we used in this study were pre-processed by the Human Connectome consortium. Here is a summary of the pipeline. The first step produced an undistorted 'native' structural volume space for each subject and aligned the T1w and T2w images using FLIRT plus a customised script. An initial brain extraction for T1w and T2w was applied using FNIRT-atlas-based-brain-mask. Next a field map distortion correction and registration of the T2w to T1w was conducted using a customised FLIRT boundary-based registration (BBR) algorithm. Next a B1 (bias field) correction was conducted using sqrt (T1w x T2w) (Feinberg et al., 2010) and registered the subject's native structural volume space to MNI space (using FLIRT linear and FNIRT nonlinear transformations). The diffusion data were collected with reversed phase-encode blips, resulting in pairs of images with distortions going in opposite directions. From these pairs the susceptibility-induced off-resonance field was estimated using a method similar to that described in Andersson et al. (2003) as implemented in FSL (Smith et al., 2004) and the two images were combined into a single corrected one (using FSL's TOPUP and EDDY functions).

The corrected data were subjected to FSL's BEDPOST (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques) algorithm [number of fibres per voxel = 3, model = 3 (deconvolution model with zeppelin), burn-in period = 3000 with rician noise] (Behrens et al., 2003, 2007).

2.2. Anatomical connectivity mapping (ACM)

To map long-range connectivity differences, ACMs were computed using FSL's probtrackx2 function (options included 50 streamlines per voxel and the mask and seed were selected to be a whole brain mask obtained using the brain extraction tool on the B0 volume) (Behrens et al., 2003, 2007). To normalise these ACMs for head size, we divided each individual's ACM by the number of voxels in their whole brain mask. The resulting image was a whole-brain connectivity map, with higher values representing a larger number of probabilistic streamlines passing through the voxel (Bozzali et al., 2011).

'Pseudo-resections' were conducted by applying exclusion masks which emulate each surgical technique. Each resection type was checked by a consultant neurosurgeon (DJC). Exclusion masks were individually drawn on the T1-weighted scan as the diffusion data were co-registered to this image. As a baseline in addition to a whole, non-resected brain, we employed a theoretically 'ideal' resection, which included a clean resection of the hippocampus and amygdala only, with no entry points from the lateral or ventral surface. These structures were identified in each individual using Freesurfer 5.3.

2.3. Testing the validity of ACM using the Papez circuit

Difference maps were calculated between whole-brain ACMs and the ACM after an 'ideal' hippocampus-amygdala-only resection. Using FSL's randomise function, one sample T-tests (corrected for multiple comparisons by using the null distribution of the max) were performed to determine where significant connectivity change (i.e., probable disconnection) occurred. We used the Juelich probability atlas to extract structures in the Papez circuit (thresholded at 25% probability) (Amunts et al., 2005; Desikan et al., 2006; Eickhoff et al., 2005; Hua et al., 2008; Mazziotta et al., 2001) and determined the extent of overlap with the areas of significant disconnection after the pseudo-resection of the hippocampus and amygdala.

2.4. Surgical pseudo-resections

In order to test systematically the effect of disconnection for different resection approaches we created a number of pseudo-resection masks. To begin with, we explored the typical range of en-bloc procedures and varied two levels (length and height) of resection in the anterior temporal lobe. Firstly, we varied the resection length from the temporal pole: 2 cm, 4 cm versus 6 cm. The exact resection length was measured for each individual using Vinci 4. A line was drawn from the lateral fissure down the entire temporal lobe. All grey and white matter in this region was removed. Secondly, we varied the resection height to include the inferior temporal gyrus (ITG) only, the addition of the middle temporal gyrus (MTG) and, finally the full height including the superior temporal gyrus (STG). Resection height was guided by the gyri; for a height only including ITG, the superior border was the inferior temporal sulcus (ITS), and for the MTG resection the superior border was the superior temporal sulcus. All grey and white matter below these superior borders was removed. This produced nine masks in total varying across both dimensions. In addition to the en-bloc procedure, we included three masks to represent the selective techniques: the trans-Sylvian, the middle temporal and the sub-temporal approaches. The trans-Sylvian mask spanned from the Sylvian fissure, across the temporal stem to the amygdala and hippocampal structures. The boundaries of the middle temporal approach were again guided by the gyri and sulci; the superior border was the STS and the posterior border was the ITS. The sub-temporal approach involved the identification of the fusiform and hippocampal gyri using the occipitotemporal sulcus as a boundary to the ITG. Thus, in total, 14 ACMs were generated for each individual. Pseudo-resections were checked by a neurosurgeon (DC). Difference maps were calculated for each of the 'pseudo-neurosurgical' methods. The 'ideal' resection was subtracted from the unresected, whole-brain ACM to determine the minimum connectivity change associated with a theoretical 'best case' scenario (amygdalohippocampectomy without any additional damage). All other 'pseudo-resected' ACMs were subtracted from the 'ideal' resection to identify the probable disconnection changes that are likely to be associated with different neurosurgical approaches to the MTL. Using FSL's randomise function, one sample T-tests (corrected for multiple comparisons by using the null distribution of the max) were performed on each set of difference maps to identify areas of reduced connectivity (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). Areas of significant connectivity change identified with these *t*-tests were overlaid with tracts from a white matter atlas (Catani & Thiebaut de Schotten, 2008) thresholded at 25% probability in order to capture individual variability in exact tract location. Average ACM scores were extracted for all white matter tracts in the natbrainlabs atlas (Catani & de Schotten, 2012) including: the anterior commissure, arcuate fasciculus, cingulum, fornix, inferior longitudinal fasciculus (ILF), Inferior Fronto-Occipital fasciculus (IFOF), internal capsule and the uncinate fasciculus. A 2×2 repeated measures ANOVA was conducted in SPSS (v.22) to test the effect of the length (distance from the temporal pole) and dorsal-ventral height of the resection on the connectivity profile across these target tracts.

3. Results

3.1. Validation of ACM

First, we validated the pseudo-surgical ACM methodology. The Papez circuit was chosen as a validation target as it is a well-understood neural system complete with known anatomical regions including the hippocampus and various long (and short) range interconnections (Papez, 1937 (Aggleton, 2008). Our aim with pseudo-surgical ACM is to reveal the disconnected regions that result from removal of target brain regions. Accordingly, if the hippocampus and amygdala are removed then we expected to reveal some, if not all, of the Papez circuit. Thus, we compared the connectivity profile after removing the hippocampus and amygdala to a whole brain ACM (Fig. 1A). As expected, this disconnected network overlapped with many regions associated with the Papez circuit (Fig. 1B–G), including the cingulum (Fig. 1B), the entorhinal cortex (Fig. 1C), fornix (Fig. 1D), mammillary bodies (Fig. 1E), anterior thalamic nuclei (Fig. 1F), internal capsule (Fig. 1G) and the retrosplenial cortex (Fig. 1H). In addition to areas within the Papez circuit, significant connectivity reduction overlapped with the ILF and the uncinate, suggesting a widespread disruption.

3.2. Disconnections associated with en-bloc resection

The second step was to determine how alternative resection approaches affect the amount and distribution of white matter disconnection. In order to explore the effect of the different neurosurgical approaches to medial temporal areas rather than resection of the MTL itself, we always compared the ACM map for each resection against the minimal baseline of an "ideal" amygdala-hippocampal only removal. We first explored the largest en-bloc anterior temporal lobectomy (6 cm from the temporal pole, including all three temporal gyri: Fig. 1A, blue region). A *t*-test of all white matter tracts within the natbrainlabs atlas revealed, as expected, a much larger area of reduced connectivity for the en-bloc resection compared to the 'ideal' baseline (Fig. 2A), which included disruption in the uncinate fasciculus (Fig. 2B), ILF (Fig. 2C) and arcuate fasciculus (Fig. 2D).

Next we systematically varied the height and length of the resection which produced nine different en-bloc resections. A 2×2 repeated measures ANOVA using Bonferroni to correct for multiple comparisons revealed a main effect of resection height on connectivity only within the uncinate fasciculus [F $(2,78) = 4.63$, $p < .05$], where a dorsally-extended resection (i.e., inclusive of MTG or MTG + STG) resulted in less connectivity (Fig. 3). We quantified the average ACM score in multiple key tracts (see Fig. 5A). The lack of significant differences in the IFOF volume of interest analysis may seem slightly surprising as the streamlines from STG and MTG regions might be expected to contribute to the ACM values in the IFOF. This probably reflects the fact that the IFOF tract is long and thus changes of value may be too small to be detected. We confirmed this outcome by splitting the IFOF, arbitrarily, into two equal volumes anterior and posterior (note this split in the VOI has no anatomical significance but rather allows us to conduct a comparison of ACM values in the anterior and posterior sections). In the anterior subdivision of the IFOF VOI, we found no significant differences in the ACM values following the ITG, MTG or STG 2 cm pseudo-resections. In contrast, there were significant differences in the posterior IFOF VOI between ITG and MTG pseudoresections [t $(39) = 2.164$, $p = .037$] and between MTG and STG [t $(39) = 2.193$, $p = .034$].

A main effect of length of resection was also found; increasing length of resection significantly reduced the connectivity score within the arcuate fasciculus [F $(2,78) = 86.75$, $p < .01$], ILF [F $(2,78) = 94.89$, $p < .01$], IFOF [F $(2,78) = 69.34$, $p < .01$] and uncinate fasciculus [F $(2,78) = -50.56$, $p < .01$] (Fig. 4). The average ACM scores for various tracts are shown in Fig. 5B.

Fig. 5 shows these results with respect the reduction in connectivity along eight major fasciculi. Given the large number of pairwise comparisons (for three levels of resection height and length), Fig. 5 shows the effect of varying resection

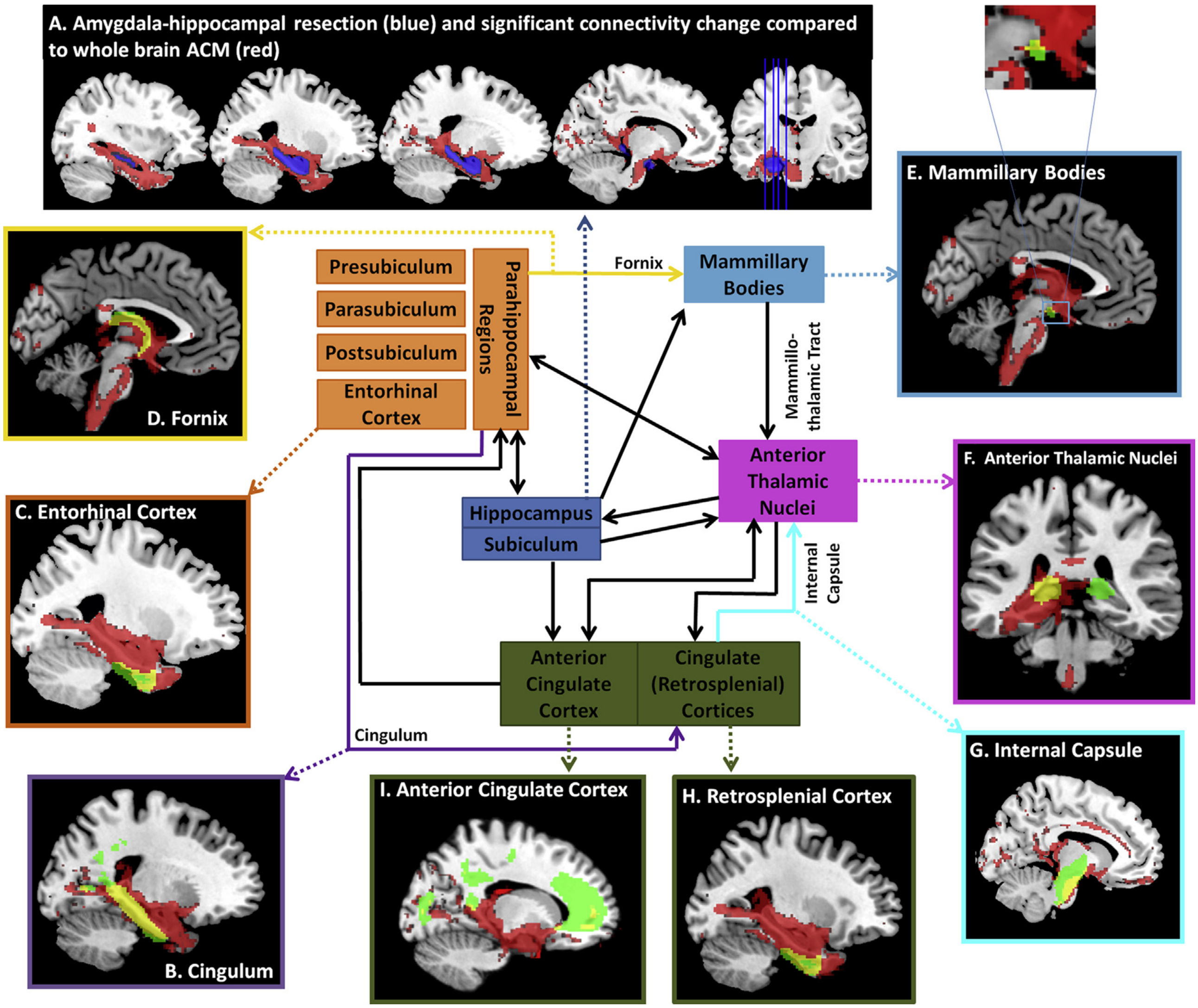

Fig. 1 – Validation of pseudo-neurosurgical ACM with respect to the Papez circuit. Adaption of the Papez circuit diagram found in Bubb, Kinnavane and Aggleton (2017). A) shows the significant connectivity reduction (red) when comparing the whole brain ACM with that for the hippocampus-amygdala resection (blue). Panels B–H show the significant connectivity change in red, areas of the Papez circuit in green and overlap between the two in yellow. B) cingulum, C) entorhinal cortex, D) fornix, E) mammillary bodies, F) anterior thalamic nuclei, G) internal capsule and H) the retrosplenial cortices, I) the anterior cingulate cortex.

height at a fixed 6 cm length (Fig. 5A) and variation of resection length including ITG, MTG and STG at all lengths (Fig. 5B). We provide the complete range of connectivity scores compared to the 'ideal' for every resection in Supplementary Material 1.

3.3. *Selective resection approaches*

Finally, we explored the effect of selective resection approaches. As before, we compared the effect of each resection approach against the amygdala-hippocampal only resection as an 'ideal' baseline. The results are summarised in Fig. 6. The middle temporal and the trans-Sylvian approaches both showed significant reductions in average ACM values in the anterior commissure, arcuate fasciculus, fornix, ILF, IFOF, internal capsule and uncinate fasciculus (all p-values<.001). In contrast, significant differences between the sub-temporal approach and the 'ideal' baseline were present only within the ILF [t (39) = 4.468, $p < .001$] and IFOF [t (39) = 3.045, $p < .004$]. We also directly compared each selective approach. Paired t-tests revealed that the sub-temporal approach had significantly higher ACM values compared to the middle temporal and trans-Sylvian approach within multiple white matter tracts (all p-values<.001), including the anterior commissure, arcuate fasciculus, fornix, ILF, IFOF, internal capsule and uncinate fasciculus. Furthermore, as expected, the selective sub-temporal procedure was associated with significantly higher connectivity within the anterior commissure, arcuate fasciculus, fornix, ILF, IFOF, internal capsule, and uncinate

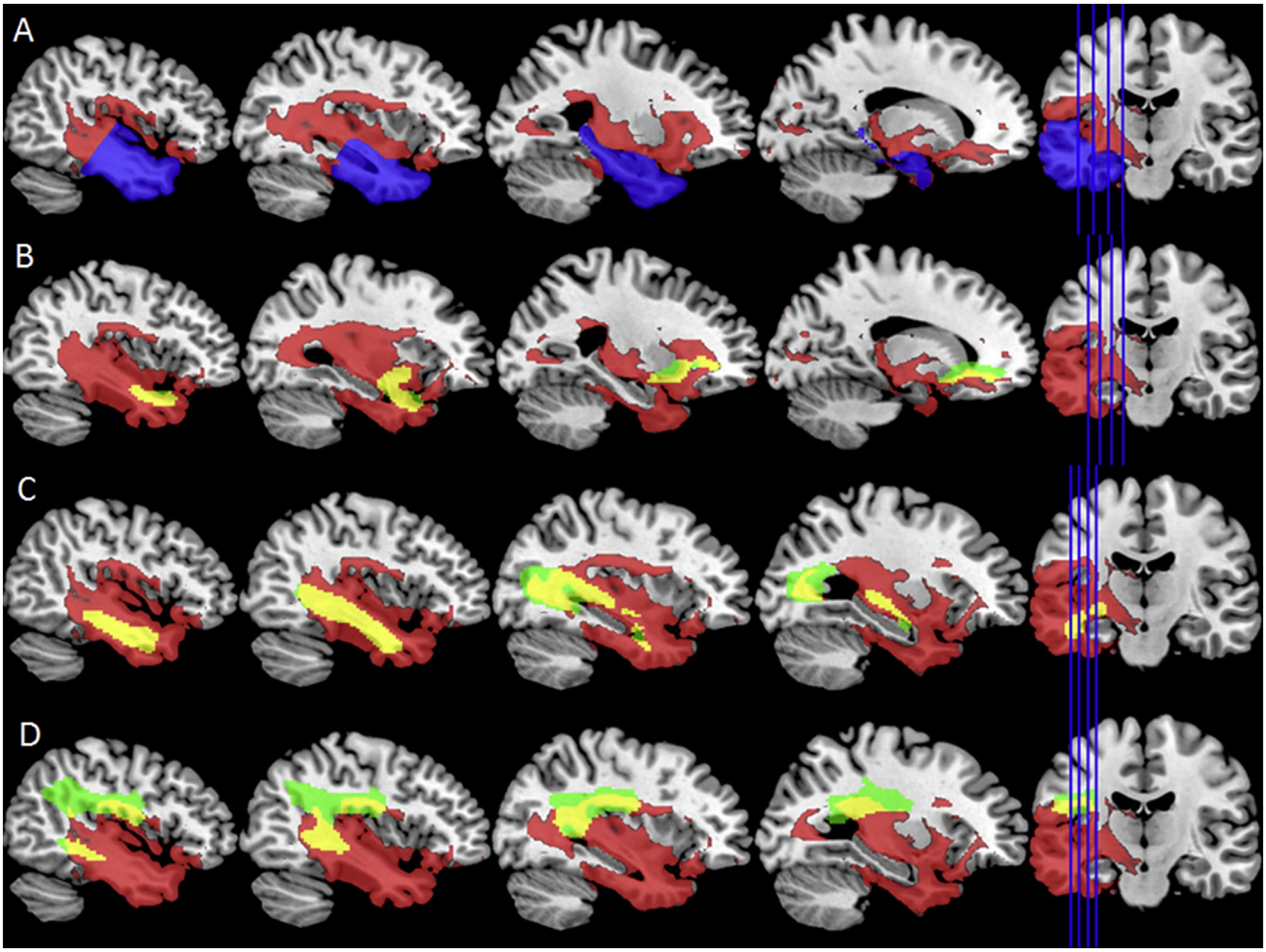

Fig. 2 – A comparison between the 'ideal' resection of only the hippocampus and amygdala, and the largest en-bloc resection of 6 cm back from the temporal pole and inclusive of all three temporal gyri. Areas of significant connectivity change are shown in red. In green are white matter tracts; B) uncinate fasciculus, C) ILF and D) arcuate fasciculus. Overlap between the reduced connectivity and tract of interest is shown in yellow.

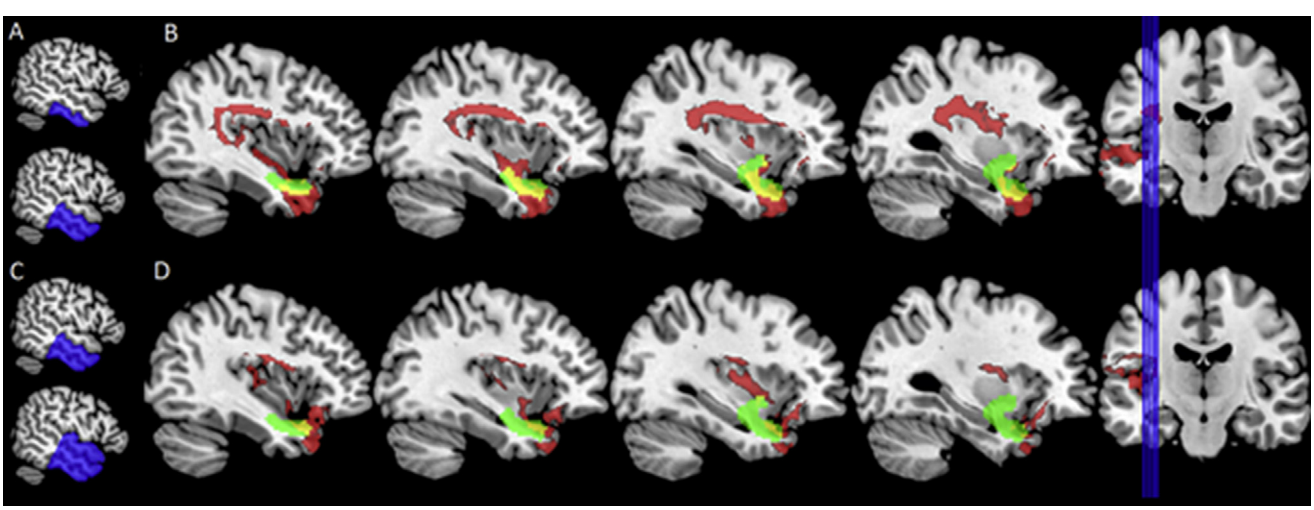

Fig. 3 – Panels A & B – comparison of ITG versus ITG + MTG approach. Panel A shows the two resections and the difference in ACM maps are shown in B. Panels C & D – comparison of ITG + MTG versus ITG + MTG + STG approach. Panel C shows the two resection regions and Panel D the ACM difference map. In Panels B & D the significant reduction in connectivity (red) is overlaid with the uncinate fasciculus (green) and overlap (yellow).

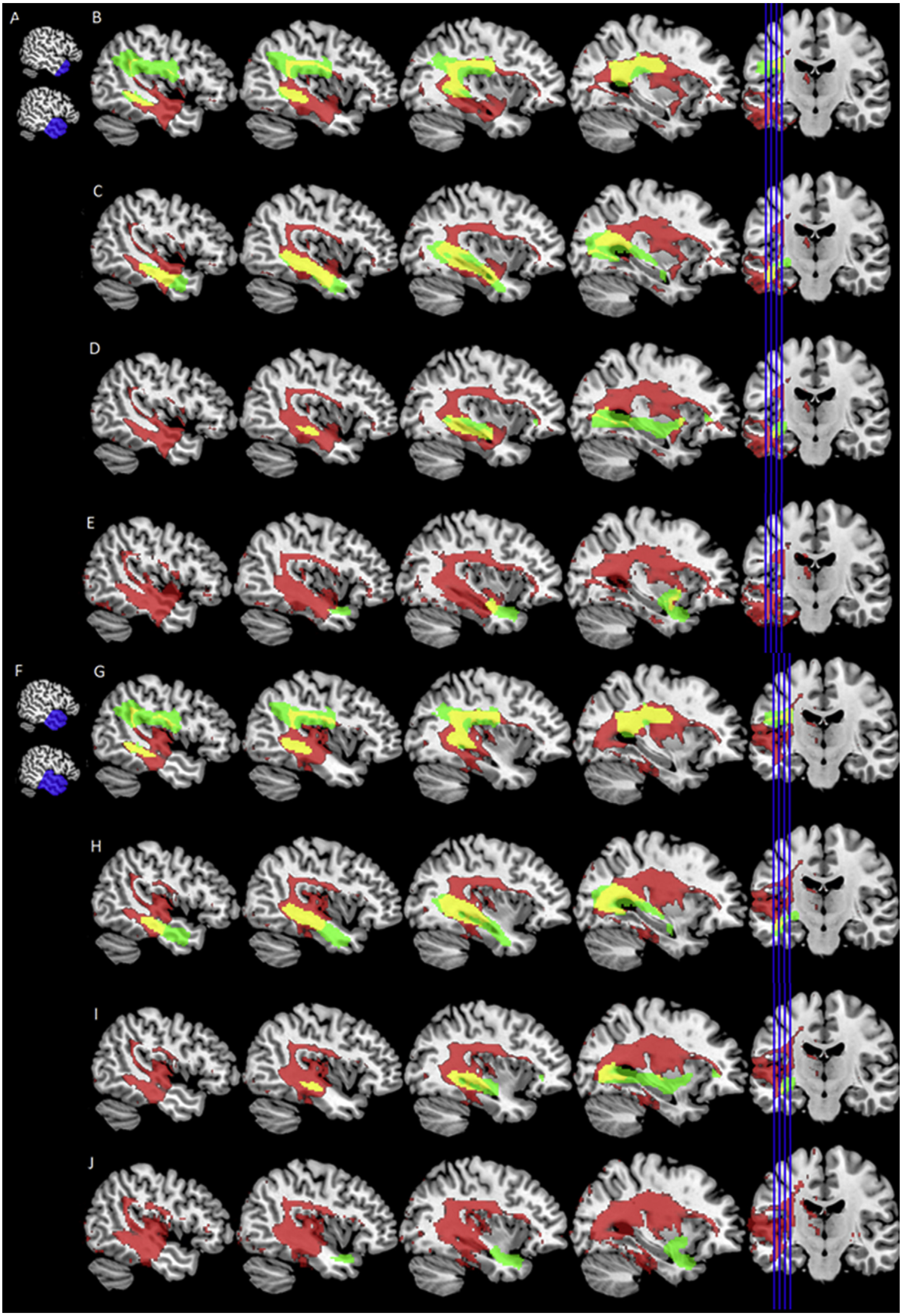

Fig. 4 – Direct comparisons of resection length from the temporal pole. A-E) Shows a direct comparison between 2 cm and 4 cm from the temporal pole (inclusive of all three temporal gyri). A: the resected areas are shown in blue. B-E show the significant connectivity reduction (red) between the two resections. White matter tracts of interest are shown in green; B)

fasciculus (all *p*-values<.001) compared to the en-bloc approaches. Significant differences between the middle-temporal and trans-Sylvian approach were more mixed, with a significantly higher ACM score in the trans-Sylvian only within the ILF [t (39) = 7.36, $p < .001$].

4. Discussion

This study systematically investigated the impact of different surgical resections on long-range connectivity using pseudo-neurosurgery. We presented a validation of the methodology and then the systematic removal of portions of the temporal lobe associated with each surgical technique. We demonstrated that both distance from the temporal pole and height of resection impacted whole brain connectivity. Selective approaches had differential outcomes on connectivity, with the sub-temporal approach producing connectivity differences most similar to the 'ideal' resection.

4.1. *Length of resection*

As expected, restricting the size of en-bloc resections results in less disconnection. In recent years, although the en-bloc approach remains the gold standard for alleviating seizures, neurosurgical practise has adapted to minimise the amount of tissue resected in an attempt to reduce postoperative decline in cognitive function (Jack et al., 1988). Traditional en-bloc anterior temporal lobectomies have been associated with various cognitive declines post-surgery, including emotion recognition (Wendling et al., 2015), verbal memory (Nascimento et al., 2016), and language and semantic memory (Lambon Ralph, Ehsan, Baker, & Rogers, 2012; Rice et al., 2015, 2018). One commonly used method is to reduce the length of the resection posteriorly from the temporal pole (Gross et al., 2015). This maximises the volume of the posterior temporal lobe preserved post-surgery. An association between length of resection and post-operative cognitive function has been reported; Amiram et al. (1989) found that a larger resection correlated with reduced verbal memory performance, and Giovagnoli et al. (2016) found that after resections measuring minimally 4.5 cm posteriorly from the temporal pole, naming performance was reduced after surgery, over and above deficits pre-surgery. Our results offer a clear explanation for these behavioural impairments; increasing the length of pseudo-resection was associated with a significant reduction in connectivity in the arcuate fasciculus, ILF, IFOF and uncinate fasciculus. The arcuate fasciculus is part of the dorsal language route (Parker et al., 2005) and plays a key role in language and naming as it connects Broca's and Wernicke's areas (Catani & de Schotten, 2012). Damage to this tract has been associated with speech production (Fridriksson, Guo, Fillmore, Holland, & Rorden, 2013; Hickok & Poeppel, 2004; Ueno, Saito, Rogers Timothy, & Lambon Ralph Matthew, 2011). Additionally, our results show that increasing resection length encroaches on the ILF and IFOF, both of which have been implicated in the semantic aspects of language processing (Bajada, Lambon Ralph, & Cloutman, 2015; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007) and the executive control of semantic processing (Binney, Parker, & Lambon Ralph, 2012) and to episodic memory (Von Der Heide, Skipper, Klobusicky, & Olson, 2013).

4.2. *Height of resection*

As well as a reduction in length of resection, more recent surgical techniques limit the temporal gyri involved, with many surgeons now preserving the STG (Spencer, Spencer, Mattson, Williamson, & Novelly, 1984). It has been suggested that preserving some of the temporal gyri may be associated with better post-surgical cognitive outcomes, with (Alpherts, Vermeulen, van Rijen, da Silva, & van Veelen, 2006) finding that a larger resection including the STG was correlated with a post-surgical decrease in verbal memory. Again, our results offer an explanation as there is reduced connectivity in the uncinate fasciculus and arcuate fasciculus as the height of resection is increased. Indeed damage to the uncinate fasciculus has been associated with semantic processing deficits (Bajada et al., 2015; Han et al., 2013) and, as noted above, the arcuate fasciculus is associated with language abilities.

4.3. *Selective amygdalo-hippocampectomies*

Although practically challenging, selective approaches remove a relatively small amount of tissue compared to the traditional en-bloc methods (Helmstaedter, 2013) in an attempt to preserve cognitive function. In post-operative comparisons of behaviour, these selective approaches were associated with better cognitive performance compared to traditional approaches, including in verbal memory (Foged et al., 2018; Hans Clusmann et al., 2002; Takaya et al., 2009) and language (Mansouri et al., 2014). Despite large differences in the tissue resected in each selective measure, few studies directly compare the clinical outcomes of these selective techniques. In a comparison of the trans-Sylvian versus en-bloc approach, Morino et al. (2006) found better preservation of memory function associated with the trans-Sylvian approach, however, verbal memory was still affected. Conversely, in comparisons of the sub-temporal approach and en-bloc approaches, the selective method was associated with preserved verbal memory post-surgery (Takaya et al., 2009). Our connectivity results show that the sub-temporal approach is associated with the least connectivity change. We suggest that the combination of better cognitive outcomes and remaining connectivity reflects preservation of the temporal stem. The temporal stem is a major white matter bottleneck through which the uncinate fasciculus and IFOF pass from the temporal lobe into the extreme and internal

arcuate fasciculus, C) inferior longitudinal fasciculus, D) inferior fronto-occipital fasciculus and E) uncinate fasciculus. Areas of overlap between the tract and connectivity change are shown in yellow. F-J show a direct comparison between 4 cm and 6 cm from the temporal pole (inclusive of all three temporal gyri). F shows the resected areas in blue. G-J show significant connectivity reduction (red) and tracts of interest (green) in the same order as the 2 cm versus 4 cm contrast.

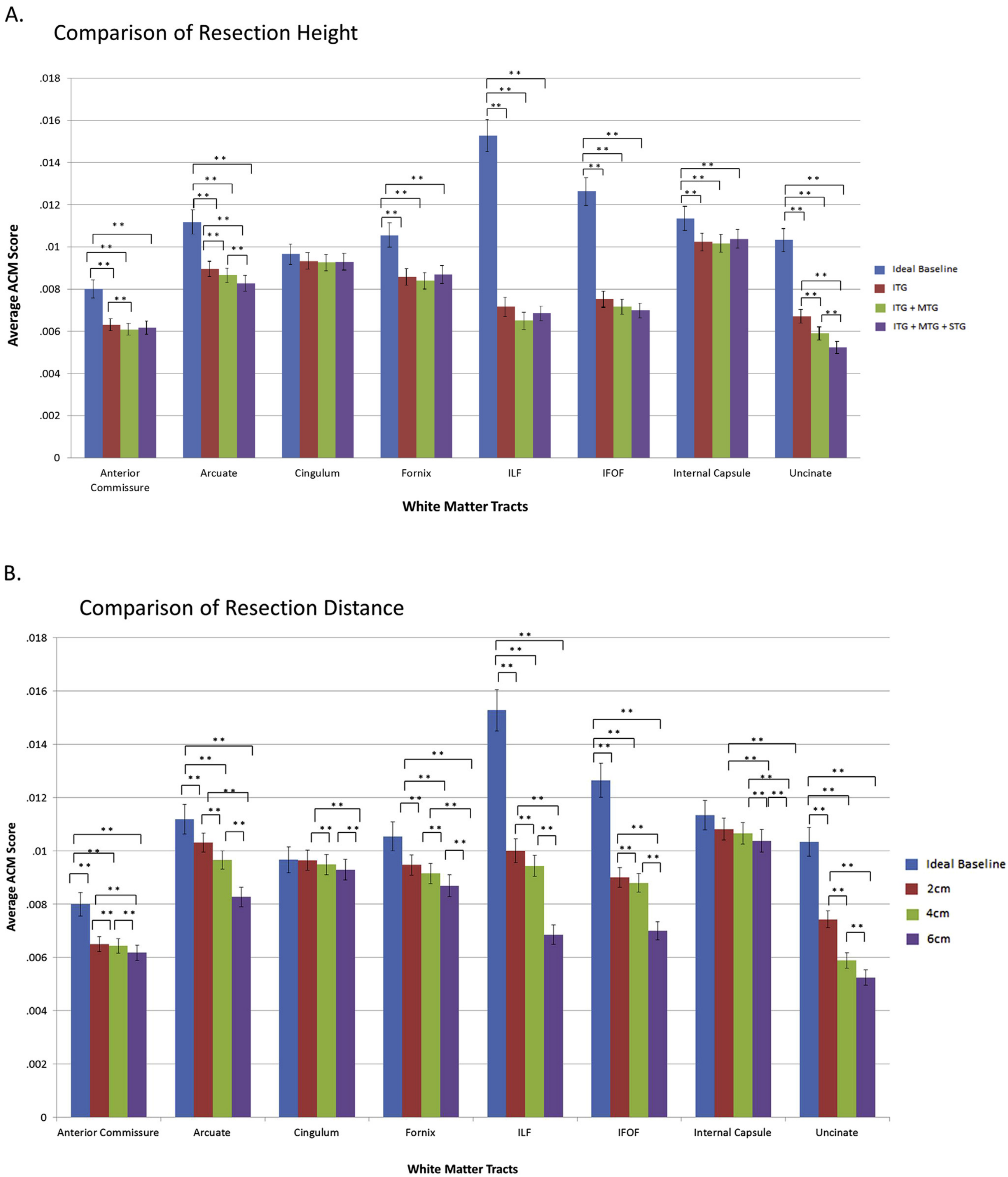

Fig. 5 – Bar plots showing the level of connectivity (streamlines normalised to brain volume) after different resection approaches within eight white matter tracts taken from the 'natbrainlabs' atlas. A) Shows a comparison of resection height between the ideal baseline of amygdalo-hippocampus only removal (blue) and resection approaches including ITG (red), ITG + MTG (green) and ITG + MTG + STG (purple) (all resections include 6 cm from the temporal pole). B) shows a comparison the effects of different resection lengths (2 cm *vs* 4 cm *vs* 6 cm: including ITG + MTG + STG at all lengths). All comparisons were corrected for multiple comparisons using Bonferroni correction. *****p* $<$ **.01, *****p*** $<$ **.05.**

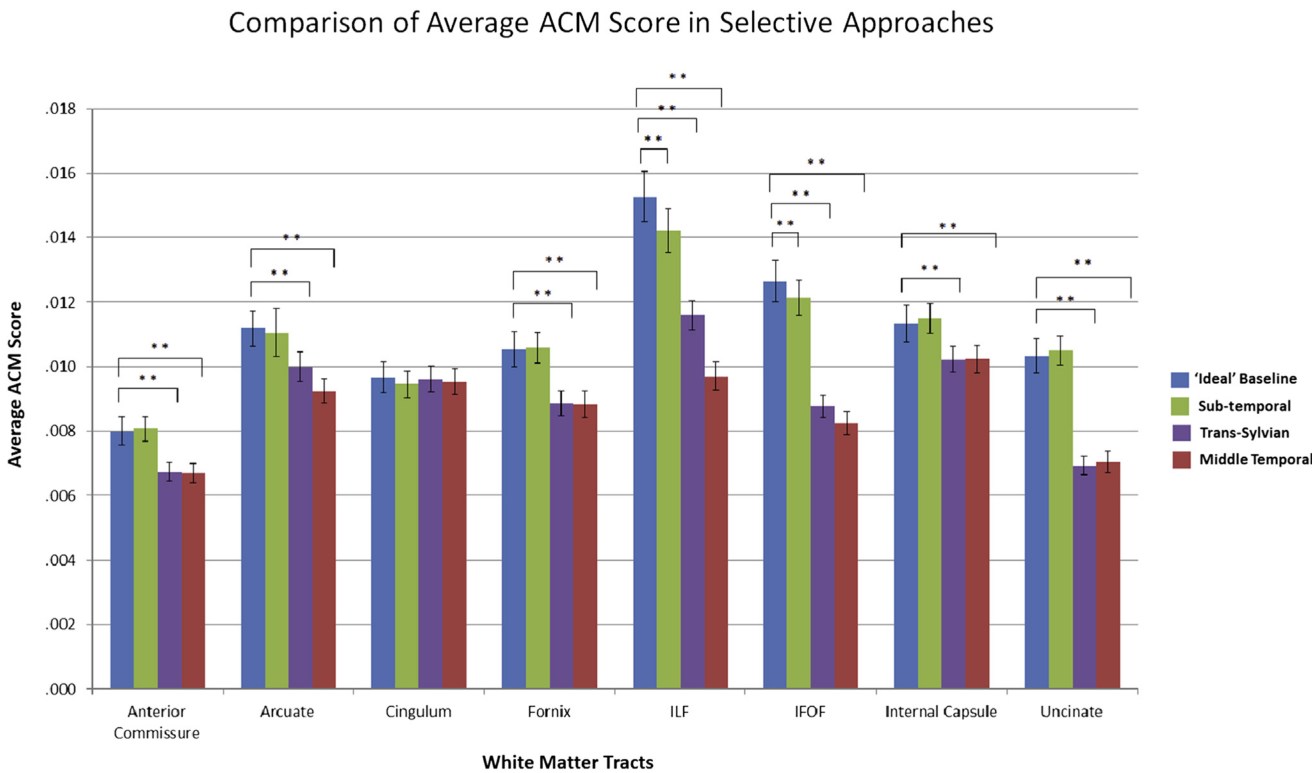

Fig. 6 – Bar plots showing the level of connectivity (streamlines normalised to brain volume) after different resection approaches within white matter tracts (taken from 'natbrainlabs' atlas). **$p < .01$.

capsules (Kier, Staib, Davis, & Bronen, 2004). Accordingly, severing this region will have a wide ranging impact on widespread fronto-temporal and occipital connectivity, and therefore behaviour (Helmstaedter, 2013). However, it is important to note the complexity of this surgical technique; large retractions of the brain are necessary resulting in a high risk of injury to the vein of Labbé (Yang et al., 2009).

4.4. 'Ideal' resection

Recent advances in technology have allowed the development of more specialised neurosurgical methods including MRI-guided stereotactic laser amygdalohippocampectomy and laser interstitial thermal therapy (Waseem et al., 2015; Kang et al., 2016) These minimally invasive approaches target the amygdala and hippocampal structures without damaging the surrounding tissue (Willie et al., 2014). These surgical methods are closest to our 'ideal' resection and, therefore, should be associated with less long-range disconnection and better cognitive function. Comparisons of this new type of surgery to traditional en-bloc methods have found significantly improved behavioural performance, specifically in naming and language tasks (Jobst, 2015), face recognition (Jobst, 2015) and verbal memory (Vojtěch et al., 2012). However, when individual patients were tested pre- and post-surgery, clinically significant decline in verbal and visual memory was still present in some patients (Greenway et al., 2017). Again our connectivity results provide an explanation for these residual deficits; even when only the hippocampus and amygdala were removed in the 'ideal' pseudo-resections, significant connectivity change was found in a number of white matter tracts, including the cingulum, ILF and uncinate fasciculus. The cingulum is a large tract connecting the frontal and temporal lobes, and has been associated with emotion and cognitive functions such as attention, working memory, verbal memory and cognitive control (Kuang, Yang, Gu, Kong, & Cheng, 2014; Taner Tanriverdi et al., 2010). This, along with the semantic language and episodic memory deficits associated with disruption to the ILF and uncinate fasciculus may explain the postsurgical behavioural deficits found even after these most conservative neurosurgical methods.

4.5. Link to surgical outcomes

Without the inclusion of patient data, definitive guidance concerning surgical outcomes cannot be made. Some important observations, however, were evident which can be explored in future research. The results indicate that connectivity change extends far beyond the site of resection and these widespread disconnection patterns vary significantly depending on both the location and extent of the resection. There is growing evidence that the major fasciculi identified as being affected by these surgical resections of the temporal lobe are associated with different aspects of language and higher cognitive functions. For example, the arcuate fasciculus is associated with phonological processing and speech production (Fridriksson et al., 2013; Sarubbo et al., 2015), the IFOF and uncinate fasciculus play a role in semantic processing (Bajada et al., 2015; Sarubbo et al., 2015), and more recently the ILF has been implicated in lexical retrieval (Herbert et al., 2018).

5. Conclusions and future directions

We have demonstrated the utility of ACMs to detect changes in whole brain connectivity, as a complementary method to existing diffusion metrics which focus on local integrity of white matter. By systematically removing tissue associated with each type of surgical resection, for the first time a direct comparison can be made between the disruption to connectivity associated with each surgical technique. As noted in the Introduction, there are multiple neurosurgical situations that require transgression of the temporal cortex. Although we have focussed on the exemplar of temporal lobe epilepsy, it should be possible to use the same methods to explore the long-range disconnections associated with other forms of resection (e.g., for access to the temporal horn, tumour resection, etc.). Identifying distant brain regions which are affected by surgery is vital to both predict and minimise cognitive deficit post-surgery. These techniques also raise the possibility of applying similar strategies at an individual level to tailor the surgical approach for an individual patient. Given that ACMs can be computed in the 'native' neuroanatomical space from individual patient's DTI, it should be possible to simulate alternative surgical approaches and their impact on long-range connectivity as a part of optimisation of neurosurgical planning. Understanding the impact of damaging long-range connections within neurosurgery is vital in order to both predict and minimise cognitive deficits post-surgery.

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Supplementary data

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