Quantitative MRI Of The Brain In Patients Undergoing Endovascular Aortic Aneurysm Repair: What Imaging Parameters Relate To Outcome?

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ABSTRACT
Background: Post-operative cognitive dysfunction (POCD) is an outcome of cardiac surgery which occurs as a result of microemboli formation and haemodynamic differences during the operation. We assess the cognition of patients who undergo Endovascular Aortic Aneurysm Repair (EVAR) prior to the operation and after the operation at 3 months and 1 year. We also sought to find the structural changes made to the brain by EVAR on the brain by acquiring and analysing multimodal MRI images from before and after the operation. Whole brain DTI measures of fractional anisotropy (FA) and mean diffusivity were assessed pre- and post-operatively.

Methods: 12 patients underwent EVAR. Neurocognitive tests were performed preoperatively (at baseline), at 3 months and 1 year after the procedure. A composite z-score for each patient was calculated from the range of subtests. A z-score of -1.5 represented post-operative cognitive dysfunction. TIW, T2W, FLAIR, DWI, DTI MRI images were acquired. FLAIR images were assessed for white matter hyperintensities using Fazekas’ scale. TIW images were segmented to tissue probability maps of white matter (WM), grey matter (GM) and cerebrospinal fluid (CSF) and then coregistered to DTI images. The FA and MD maps were masked according to the native tissue types (GM, WM and CSF). Whole brain histograms were extracted of the FA of WM, MD of GM and MD of WM. The Wilcoxon signed-rank test was used to assess whether there was a significant difference between the z-scores at baseline and at 3 months, the z-scores at baseline and at 1 year and the z-scores at 3 months and at 1 year. We also used the Wilcoxon signed-rank test in order to assess for changes in the means of FA (of white matter), MD (of grey matter) and MD (of white matter) pre- and post-operation.

Results: We found a significant improvement between the z-score for global cognition at 3 months compared to baseline. There was no significant difference between the z-scores at baseline and at 1 year nor between the z-scores at 3 months and at 1 year. The 2 patients with extensive white matter hyperintensities (high-scoring on Fazekas’ scale) improved cognitively. No significant difference was found between the FA of white matter before and after the operation and there was no significant change in the MD (of grey matter) and the MD (of white matter) pre and post-operation. Conclusions: These results suggest, with a small patient sample, that POCD is not a certain outcome after EVAR. The results we gained with whole brain FA and MD also suggest that the procedure makes little to no structural changes to the brain at an early post-operative time point. Further investigation of this topic with a larger patient sample and a longer time period of cognitive testing would increase the reliability of the results found in this study.

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1. INTRODUCTION

Post-operative cognitive decline is a long-term effect of cardiac surgery procedures. (Newman et al., 2001; Tan & Amoako, 2013; Wilson et al., 2008). Surgery may cause neurological complications due to cerebral ischaemia caused by hypoperfusion, microemboli formation or a combination of both. Anaesthetics in surgery can cause cerebral hypoperfusion due to poor haemodynamics. Cerebral hypoxaemia during cardiac surgery was found to be a severe risk factor for post-operative delirium (Palmbergen et al., 2012; Slater et al., 2009), supporting suggestions of the role cerebral desaturation may play in cognitive decline. This project aims to assess cognitive decline and brain structural changes (visualised by MRI) in patients undergoing endovascular aortic aneurysm repair.

1.1 Aneurysms

An aneurysm is an excessive localised swelling of an arterial wall. Aneurysms may be diagnosed by ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI), angiography and in the case of an abdominal aortic aneurysm, at a late-stage by palpation during a physical examination. Aneurysms may obstruct blood flow to vital regions of the body including the brain and as echocardiographic studies in atheromatous disease indicate, they can be associated with the occurrence of silent cerebral ischaemic events (Djaiani et al., 2004) and stroke (Goto et al., 2003). Ischaemic lesions (dark spots on diffusion weighted imaging) can correlate with cognitive decline (Wilson et al., 2008).

Surgery is a viable option when the risk of rupture for an abdominal aortic aneurysm (AAA) exceeds the risks of surgical repair. This occurs when the aneurysm is thicker than 5.5cm (McMonagle & Stephenson, 2014). Rupture can result in internal bleeding, which without adequate management leads to shock or death.

Management of an aneurysm pre-rupture can be by medical therapy or surgery. Medical therapy aims at controlling blood pressure by smoking cessation and statin use (Rentschler & Baxter, 2007) to reduce the rate of aneurysm expansion. Surgical treatment options are conventional or endovascular aortic aneurysm repair (EVAR). Endovascular stent grafts are recommended by NICE guidelines if the aneurysm is below the kidney, has not burst and the risks and benefits of the procedure have been discussed with the patient (NICE, 2009).

1.11 Endovascular aortic aneurysm repair

EVAR has been preferred over conventional treatment because it avoids transperitoneal manipulation, reducing the period of aortic occlusion to allow a faster recovery from the repair procedure (Thompson et al., 1997). EVAR consists of fitting a stent which permits blood flow through the region without encountering the aneurysm.

Manipulation in the aneurysm sac during EVAR can lead to huge microembolisation. An embolism is an obstruction in a blood vessel due to a blood clot or other foreign matter which has travelled there via the bloodstream from another region of the body. In comparison with conventional aneurysm repair, EVAR has been proven to cause greater peripheral embolization (Thompson et al., 1997).

Transfemoral aortic valve implantation (TAVI) (for aortic stenosis) is another procedure linked with post-operative cognitive dysfunction. Neurological injury from TAVI is marked by the presence of acute cerebral ischaemic lesions secondary to microemboli on diffusion-weighted imaging (DWI) after the surgery (Allassar et al., 2015). TAVI is associated with a high rate of clinically silent cerebral embolism (72.7%) (Ghanem et al., 2010) and an incidence of clinically apparent cerebral ischaemia ranging between 0.6% and 10% (Grube et al., 2007; Webb et al., 2009; Zajarias & Cribier, 2009). Device positioning (the passage of a stenotic aortic valve with the catheter) and implantation (the insertion of the new valve) are associated with the greatest amount of embolic signals (Allassar et al., 2015; Ghanem et al., 2010). Emboli are detected as high intensity short duration signals on a tran cranial doppler ultrasound performed during surgery.

1.2 MRI Imaging

MRI imaging is used pre- and post-surgery to detect structural brain changes.

1.21 Standard Clinical MRI

FLAIR, DWI and T2W are the main sequences used clinically. FLAIR MR is an inversion recovery technique which combines T1 and T2. The inversion time (TI) is set to the zero crossing point of cerebrospinal fluid (CSF), erasing the signal from the fluid (Okuda et al., 1999). FLAIR
MR permits greater visibility to abnormalities in structure indistinguishable by T1W and T2W imaging. In this study, FLAIR distinguishes oedema in T2W images. FLAIR imaging nullifies the signal from the CSF (bright in T2), increasing the image contrast and making hyperintense lesions more apparent. One study found white matter hyperintensities to be associated with a decline in executive function and processing speed (Jokinen, 2005). FLAIR MR can display white matter hyperintensities from pre- and post-operative scans which may relate with cognitive changes.

The T2-weighted imaging MRI signal depends on the T2 relaxation time, which is the time taken for the decay of the MRI signal and the loss of the M_zy component of the magnetic vector. In T2W, fat appears dark whilst CSF and water appear brightest because of a longer relaxation time. Oedema and cellular necrosis can increase T2 by increasing water in the brain. Cerebral microbleeds (areas of low signal less than 10mm wide) can reduce T2 due to Fe product release. Microbleeds were thought to be clinically silent (Kwa et al.,1998) but recent evidence points towards an impact on cognition (Werring et al., 2004).

Diffusion-weighted imaging is used routinely in clinics as a sensitive method of detecting acute stroke. DWI measures the diffusion, microscopic motion of water in tissue, within the brain structure. Time, viscosity, barriers and molecular size affect the extent of diffusion which is quantified by the Einstein diffusion equation:

\begin{equation}
< r^2 >= 6Dt
\end{equation}

\( r= \) root mean squared displacement (measure of distance) \( D= \) diffusion coefficient (can be influenced by viscosity, barriers and molecular size). \( t= \) time over which the molecule diffuses

Water diffusion in tissue is altered in disease. In acute stroke, cytotoxic oedema reduces the extracellular space and MD is decreased. In chronic stroke, cellular necrosis increases the extracellular space and MD increases. On DW-MRI, increased diffusion creates a low signal. DWI can show additional lesions caused by surgery. A previous study found that cardiac surgery increases the number of ischaemic lesions found on DWI (Knipp et al., 2005). Formation of new lesions due to surgery may coincide with a decline in cognition (Maggio et al., 2013).

1.22 WMH lesions

Microemboli have been observed to be associated to white matter hyperintensity (WMH) lesions on MRI (Altaf et al., 2006). WMH lesions are regions of high intensity in the white matter found in the T2-weighted image. Lesions can represent ischaemia, oedema and inflammation in the white matter structure and are hyperintense because of an increase in fluid in the brain structure which increases T2 relaxation time and the signal. WMH lesions can also be formed as a consequence of cerebrovascular disease. WMHs may arise secondary to aneurysms as a result of cerebral small vessel disease (cSVD). cSVD may cause WMHs by the progression of arteriolosclerosis to luminal narrowing, progressive stenosis and chronic diffuse hypoperfusion (Gunda et al., 2012). Chronic hypoperfusion in cSVD causes diffuse tissue disintegration due to demyelination and axonal damage. This outcome is visualised as WMHs on T2W and FLAIR imaging. In addition to diffuse WMHs, cSVD appears in radiological imaging as lacunar infarcts (leukoaraisiosis) (Lawrence et al., 2013).

Several studies have linked WMHs with deficits in executive function, processing speed, memory and visuospatial functions (Benedictus et al., 2015; Jokinen, 2005; Lawrence et al., 2013). White matter damage is suggested to relate with cognitive dysfunction as a result of white matter tract disruption and the disconnection of the cortical-subcortical and cortical-cortical underlying networks which play a role in cognition (O’Sullivan et al., 2001). The positive correlation found between the severity of WMHs and decline in memory, attention, executive function and global cognition in patients with subjective cognitive decline supports the idea (Benedictus et al., 2015).

1.23 Advanced MRI

The advanced MRI sequences which are mainly used in research studies are T1-weighted (3D high resolution) and diffusion tensor imaging (DTI).

In T1W images, the MRI signal generated depends on the T1 relaxation time of tissues. T1 relaxation time is the time taken for the recovery of the z magnetisation which is lost during the generation of the MRI signal. In T1W, fat appears bright and fluid appears dark. Increased water as a result of inflammation or oedema in a region increases T1 relaxation time. Paramagnetic substances (eg. Fe released in haemorrhage) and calcification increase brightness because they
reduce T1 relaxation time and proton density in the image region. T1W is useful for showing normal soft-tissue anatomy and fat. In this study, the 3D T1 image plays a key role in the segmentation of the grey and white matter.

DTI is increasingly used in research studies of cognitive dysfunction for mapping the anisotropy of water diffusion in the brain tissue and finding changes in brain structure due to white matter damage in disease. The diffusion tensor is measured by computing the apparent diffusion coefficient (ADC) in six different gradient orientations and with no gradient. A 3D model called the Diffusion Tensor model is built of the diffusion at each image voxel. The diffusion tensor is a 3x3 covariance matrix which describes the covariance of diffusion displacements in 3D normalised by the diffusion time and shown by the equation below:

\[
D = \begin{bmatrix}
D_{xx} & D_{xy} & D_{xz} \\
D_{yx} & D_{yy} & D_{yz} \\
D_{zx} & D_{zy} & D_{zz}
\end{bmatrix}
\]

(2)

The diffusion tensor can be visualised by an ellipsoid which shows the three principle eigenvectors (diffusion directions) and their eigenvalues (their magnitudes). Eigenvalue magnitudes can be affected by changes in local tissue microstructure in disease (Alexander et al., 2007). Figure 6 shows the two types of diffusion tensor shapes.

Two parameters given by DTI which may be indicative of cognitive dysfunction in patients if abnormal are fractional anisotropy (FA) and mean diffusivity (MD). FA is a value between zero and one which describes the degree of anisotropy of diffusion (see Figure 7). FA can be quantified by the equation below.

\[
FA = \sqrt{\frac{1}{2}(\lambda_1-\lambda_2)^2+(\lambda_1-\lambda_3)^2+(\lambda_2-\lambda_3)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}
\]

(3)

MD quantifies the extent of diffusion by calculating the mean of the three eigenvalues. It can be quantified by the following equation (see Figure 8).

\[
MD = \frac{\lambda_1+\lambda_2+\lambda_3}{3}
\]

(4)

FA and MD are quantitative parameters which can be calculated with the aim of assessing whether they can be associated with clinical outcomes in cognition domains. Charlton et al found changes in FA and MD to relate with declines in executive function, working memory and processing speed domains. White matter damage was shown by a reduction in FA and increased MD in correlation with reduced cognitive scores (Charlton et al., 2006).

In this study, we are using the T1W, T2W, FLAIR, DWI and DTI sequences.

1.3 Scoring systems in the analysis of images

A majority of past MRI studies on the brain have analysed images qualitatively with the use of scoring systems. A major system used in scoring is the Fazekas’ scale (Fazekas et al, 1987):

<table>
<thead>
<tr>
<th>Score</th>
<th>Periventricular lesions</th>
<th>White matter lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No lesions</td>
<td>No lesions</td>
</tr>
<tr>
<td>1</td>
<td>Caps or thin line</td>
<td>Punctate foci</td>
</tr>
<tr>
<td>2</td>
<td>Smooth halo</td>
<td>Beginning confluence of foci</td>
</tr>
<tr>
<td>3</td>
<td>Extension into the white matter</td>
<td>Large confluent areas</td>
</tr>
</tbody>
</table>

Scoring systems allow us to assess the structure of the patients’ brains by giving numerical scores to them. In their use, we can attempt to find an association between scoring high (increased structural brain damage) in these systems and cognitive decline displayed by psychometric testing.

Scoring systems possess various disadvantages: they give qualitative measures, ordinal data, require non-parametric statistics and are to an extent subjective to the scorer. We look to see whether objective quantitative data from DTI measures will be more sensitive than visual scoring systems. We will be using whole brain histogram data because we desire to assess global changes in MD and FA which can be predictive of cognitive decline. This novel aspect makes this project different from past studies on cognitive decline in cardiac surgery patients. Also, past studies assessing leukoaraiosis and vascular cognitive impairment have shown that whole brain histograms are more sensitive tools in detecting brain structure changes than visual MRI (Della Nave et al., 2007; Zhou et al., 2008)

Psychometric testing is used to assess the clinical impact which surgery may have on patients. A range of cognitive domains are assessed. MRI data can be used to help in understanding the aetiology of cognitive decline. Statistical analysis will be performed to inspect the suspected correlation between whole brain
histogram parameters and decline in cognitive scores.

1.4 Hypotheses

Many patients will have pre-existing white matter hyperintense lesions caused by vascular disease. We believe these patients will be more sensitive to the impact of emboli and anaesthetics during EVAR therefore we have made the following hypotheses for this project:

1. Certain pre-treatment characteristics will potentiate a worse cognitive outcome
   a. Patients who score higher on Fazekas’ scale for WMLs on their pre-operative FLAIR image will have lower test scores at 3 months and 1 year compared to baseline.
2. EVAR will cause hypoxic insults which lead to structural changes in the brain detected by MRI imaging
   a. There will be a reduction of mean FA and increase in mean MD from the whole brain histograms post-operation compared to pre-operation. (DTI)

2. METHODS

Ethical approval for this study was obtained on the 7th of May 2013 from the NRES committee London-Riverside.

2.1 Inclusion Criteria

Any patient, aged 18 and above, admitted to St George’s Hospital with an abdominal or thoracic aortic aneurysm who would undergo endovascular repair under general anaesthetics.

Patients who underwent the repair of a common iliac aneurysm using a bifurcated graft were also included due to the identical procedure involved and the similarity in the pathophysiology of a common iliac aneurysm and an abdominal aortic aneurysm (wall structure change because of atherosclerotic disease and hypertension).

All patients were required to give consent for inclusion in the study.

2.1.1 Exclusion criteria

Patients who were excluded from the study fulfilled one or more of the following conditions:

1. Unable to give consent for inclusion in the study,
2. Incapable of completing the battery of cognitive function tests to a satisfactory standard (e.g. due to loss of vision or hearing during testing)
3. Presented with acute clinical instability,
4. Underwent open repair or repair under local anaesthetic
5. Deemed by MRI safety criteria to be unsafe for scanning

2.2 MRI Acquisition

MRI scans were performed pre- and post-operatively using a Philips 3-Tesla dual Tx Achieva machine. The pre-operative scan was performed within 14 days prior to the surgery. The post-operative scan was made within 14 days after the surgery. All data was acquired with a 32 channel head coil in dual Tx mode. The protocol lasted 20 minutes and included the following scan sequences which each provided whole head coverage:

1. Diffusion weighted imaging sequence (DWI): repetition time (TR)= 2769ms echo time (TE)= 52ms, 32 slices of 5mm thickness, resolution: 2.05mm x 2.55mm
2. Fluid attenuated inversion recovery (FLAIR): repetition time (TR)= 11000ms echo time (TE)= 125ms inversion time (TI)= 2800ms, 32 slices of 5mm thickness, resolution: 0.99mm x 1.02mm
3. T2-weighted turbo-spin-echo (T2W-TSE): repetition time (TR)= 3000ms echo time (TE)= 80ms, 32 slices of 5mm thickness, resolution: 0.99mm x 1.0mm
4. T1-weighted 3D turbo-field-echo (T1-3D-TFE): repetition time (TR)= 7.9ms echo time (TE)= 3.9ms flip angle= 8 degrees, resolution: 1mm x 1mm x 1.5mm
5. Diffusion tensor imaging sequence: repetition time (TR)= 6000ms echo time (TE)= 70ms, 48 slices of 2.5mm thickness, resolution: 2.5mm x 2.5mm x 2.5mm, b-factor: 1000, data acquired with 6 diffusion directions

All sequences were obtained in the axial plane except for the T1W image taken in the sagittal plane for better segmentation. All data was anonymised for storage on the university computers before analysis.

2.2.1 Obtainment of images

Each patient’s images in all five modalities were obtained from the PACS system. MRIconvert was used to convert the raw DICOM images to the .nii format suitable for analysis.
Figure 10: DTI processing pipeline. Alphabetical explanation of images.
(a) T1W image. (b) Tissue probability maps of grey matter, white matter and cerebrospinal fluid (CSF) from left to right. (c) DTI image with diffusion sensitisation of $b=0$ on the left and T1W image on the right. (d) FA map masked according to white matter (e) MD map masked according to grey matter and white matter (from left to right) (f) Whole brain histograms for FA of WM, MD of GM and MD of WM (from left to right)

The pre-operative FLAIR images were viewed using the FSL program with their WMHs scored according to Fazekas’ scale (See Figure 9 for examples). We can see whether a high score on Fazekas’ before surgery predisposes to post-operative cognitive decline.
2.22 DTI processing

T1W images were segmented using the ‘segment’ function of SPM8 (Statistical Parametric Mapping) (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). SPM was run in matlab and utilises the average whole brain probability map of normal volunteers (atlas-based) to provide a good segmentation. T1 images were segmented without skull stripping or re-orienting the image from the sagittal plane in order to achieve good segmentation which resulted in the formation of tissue probability maps of grey matter (GM), white matter (WM) and cerebrospinal fluid (CSF) for the whole brain. Within tissue probability maps, each pixel has a value between 0 and 1 indicating the likelihood of each tissue type in that location.

The T1 and the segmented probability maps were coregistered to the DTI by the use of the ‘coregister (Estimate and Reslice)’ function of the SPM software. In the software, the ‘reference’ file for coregistration was the base DTI image (the data acquired at b=0 with no diffusion weighting). The ‘source’ file used was the T1 weighted image whilst the segmented probability maps of GM, WM and CSF were added as the ‘other’ files because they have the same orientation as the original T1 weighted image.

Coregistering was also performed on the remainder of MRI data. FLAIR and T2 images were coregistered to DTI by the use of FLIRT (FMRIB’s Linear Image Registration Tool). Coregistration was necessary for the realignment of inconsistencies between intra-subject images generated by motion. Images for each protocol have different in-plane resolution and numbers of slices. The process includes reformatting to make these features consistent. Higher resolution images can be down-sampled, or lower resolution images adjusted to give a higher resolution in order to enable the alignment needed for further processing to proceed.

The FSL Linear Image Registration Tool (FLIRT, FMRI Software Library, FSL version 4.1; FMRIB Analysis Group, Oxford, UK, http://www.fmrib.ox.ac.uk/fsl) was used to mask the various parametric DTI maps according to the tissue types (GM, WM, CSF) by combining the segmented maps of the T1 image with the FA and MD maps. Masked images were created with the probability threshold of 0.5. At this threshold, specific tissue types within the tissue probability map are only assigned for voxels with the probability of 0.5 or greater for the tissue type.

Fiji (Fiji is just imageJ) (http://fiji.sc/Fiji) software was used to extract whole brain stack histograms for MD, FA and q within the grey matter, white matter and cerebrospinal fluid from the thresholded masked images.

The ranges set for the FA and MD values in the whole brain histograms were as follows: FA: 0.001 to 1 MD: 0.0001 to 0.003cm²s⁻¹

For the ranges, the lower bound was used to exclude the background pixels at 0 and the higher bound was made to be higher than the highest expected value. A fixed range was also necessary in order for us to combine data from different patients.

2.3 Cognitive Testing

Patients underwent cognitive testing (performed by Dr R Benson) between 1 and 7 days pre-operatively, and at 3 months and 1 year post-operatively. Tests were given upon consent and lasted 40-50 minutes to assess cognitive function in a variety of domains. Results were anonymised to prevent marking bias.

The Wechsler test of adult reading was used to assess the baseline measure of patient’s premorbid intelligence. The short mini mental state examination was used to assess the mental orientation of the patients. Patients scoring below 24 would be excluded from the study due to possible dementia.

The repeatable battery for the assessment of neuropsychological status (RBANS) was used to measure change across immediate memory, visuospatial ability, language, attention and delayed memory. These tests were advantageous for detecting and tracking changes over time. Versions A and B of the tests were used. Version A was used before the surgery and 12 months after the surgery. Version B was used 3 months after the surgery. Different versions of the tests were used in order to account for a learning effect. 12 months between the initial testing and re-testing with version A was thought to be enough to prevent the learning effect causing an influence on the scores.

For an estimate of general cognitive ability and executive functioning, the Wechsler abbreviated scale of intelligence was used. Trails tests A (visual attention, visual search speed and speed of processing) and B (mental flexibility and executive function) were included. Test B is suggested to be highly sensitive to frontal lobe damage.
Patient mood was tested by the Hospital Anxiety and Depression scale. In this scale, patients were asked to rate their experiences from 0 to 3 of statements in relation to anxiety eg. ‘I feel tense or wound up’ and depression eg. ‘I feel cheerful’. Their scores in the HADS category can be used to assess whether their mood has impacted their scores in other domains.

2.4 Statistical Analysis

For each test, we calculated the general mean and standard deviation at baseline for all the patients. These values were then used in order to create a z-score. A z-score is a measure of how different an individual score is from the group mean. In this case, the z score is the difference in test score at 3 months or one year in comparison to the mean at baseline (prior to surgery). A z score of -1.5 is defined as post-operative cognitive dysfunction (Rappold et al., 2016).

The z-scores for each patient in each test at baseline, 3 months and 1 year after surgery except for the Trails were calculated by using the formula:

\[ Z = \frac{\text{Score at baseline} - \text{mean at baseline}}{\text{standard deviation}} \]  
\[ Z = \frac{\text{Score at 3 months or 1 year} - \text{mean at baseline}}{\text{standard deviation}} \]  

The z-scores for the Trails tests were calculated by an inverted formula because the test scores in them were based on the time taken to perform tasks. This way, a positive z-score shows an improvement and a negative z-score stipulates a decline in cognition for all of the test types.

The average z scores in all the subtests for each patient at baseline, 3 months and 1 year were calculated.

2.41 Wilcoxon signed-rank test

We used GraphPad Prism (www.graphpad.com/scientific-software/prism) to run two-tailed Wilcoxon signed-rank tests with the data. The Wilcoxon signed-rank test is a non-parametric test which compares the results in the two time points, according to their population mean ranks, in order to test the null hypothesis that there is no difference between them against an alternative hypothesis which deems one group larger than the other. The test provides a P value which would have to be less than 0.05 to show a significant difference between the two time points considered.

1. We used the test in order to investigate whether there is a significant difference between:
2. The Z-scores at baseline and at 3 months
3. The Z-scores at baseline and at 1 year
4. The Z-scores at 3 months and at 1 year

The means of FA (of white matter), MD (of grey matter) and MD (of white matter) pre- and post-operation.

2.5 Reproducibility Studies

We took brain MRI images of 4 healthy volunteers in order to assess how consistent the FA and MD were across two time points. We followed the protocol described above for their images.

3. RESULTS

3.1 Cognitive Test Scores

Table 1 lists the z-scores for global cognition. No patient developed global cognitive dysfunction (z-score of -1.5).

<table>
<thead>
<tr>
<th>Table 1 Z-scores for Cognitive Tests</th>
<th>Baseline</th>
<th>3 months</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAAOP001</td>
<td>0.74</td>
<td>0.26</td>
<td>0.52</td>
</tr>
<tr>
<td>AAAOP002</td>
<td>-0.90</td>
<td>-0.31</td>
<td>-0.87</td>
</tr>
<tr>
<td>AAAOP003</td>
<td>-0.45</td>
<td>0.00</td>
<td>-0.01</td>
</tr>
<tr>
<td>AAAOP004</td>
<td>-0.10</td>
<td>0.05</td>
<td>0.34</td>
</tr>
<tr>
<td>AAAOP005</td>
<td>-0.48</td>
<td>-0.38</td>
<td>-0.41</td>
</tr>
<tr>
<td>AAAOP006</td>
<td>0.84</td>
<td>0.85</td>
<td>0.47</td>
</tr>
<tr>
<td>AAAOP009</td>
<td>0.18</td>
<td>0.21</td>
<td>0.55</td>
</tr>
<tr>
<td>AAAOP013</td>
<td>0.42</td>
<td>0.81</td>
<td>0.60</td>
</tr>
<tr>
<td>AAAOP019</td>
<td>0.21</td>
<td>0.60</td>
<td>0.97</td>
</tr>
<tr>
<td>AAAOP036</td>
<td>-0.26</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>AAAOP037</td>
<td>-0.02</td>
<td>0.54</td>
<td>0.78</td>
</tr>
<tr>
<td>AAAOP096</td>
<td>-0.17</td>
<td>-0.08</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>0.00083</td>
<td>0.22</td>
<td>0.29</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>0.51</td>
<td>0.41</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Blank spaces denote missing test data for patients ‘36’ and ‘96’ after 1 year of surgery.

Figure 11 displays a line chart of the z-score at baseline to 3 months. 6 patients visibly show significant improvements, one shows a significant decline and the remainder show steady changes.
Figure 11: Z-scores at baseline and at 3 months. We found a significant improvement between these two time points.

The Wilcoxon signed-rank test showed a significant improvement in cognition (P value of 0.021) from baseline to 3 months. No significant difference in cognitive test scores (P value of 0.8457) was found between scores at 3 months and 1 year. No significant difference was also found between scores at baseline and 1 year (P value of 0.0645).

### 3.2 Measures for DTI Parameters

Results for FA of white matter, MD of grey matter and MD of white matter pre and post-operation extracted from whole brain histograms are shown in Table 2 below. Figures 12-14 display line charts.

<table>
<thead>
<tr>
<th></th>
<th>AAAOP001</th>
<th>AAAOP002</th>
<th>AAAOP003</th>
<th>AAAOP004</th>
<th>AAAOP005</th>
<th>AAAOP009</th>
<th>AAAOP013</th>
<th>AAAOP019</th>
<th>AAAOP036</th>
<th>AAAOP037</th>
<th>AAAOP096</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean FA of WM</strong></td>
<td>0.36</td>
<td>0.33</td>
<td>0.34</td>
<td>0.36</td>
<td>0.29</td>
<td>0.37</td>
<td>0.32</td>
<td>0.35</td>
<td>0.97</td>
<td>1.00</td>
<td>1.04</td>
</tr>
<tr>
<td><strong>Post op</strong></td>
<td>0.27</td>
<td>0.34</td>
<td>0.26</td>
<td>0.28</td>
<td>0.29</td>
<td>0.36</td>
<td>0.31</td>
<td>0.35</td>
<td>1.01</td>
<td>1.04</td>
<td>1.04</td>
</tr>
</tbody>
</table>

Table 2

Means for the FA and MD DTI parameters before and after surgery (Pre and post)

<table>
<thead>
<tr>
<th></th>
<th>AAAOP001</th>
<th>AAAOP002</th>
<th>AAAOP003</th>
<th>AAAOP004</th>
<th>AAAOP005</th>
<th>AAAOP009</th>
<th>AAAOP013</th>
<th>AAAOP019</th>
<th>AAAOP036</th>
<th>AAAOP037</th>
<th>AAAOP096</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean MD of GM</strong></td>
<td>0.35</td>
<td>0.95</td>
<td>0.98</td>
<td>0.95</td>
<td>0.96</td>
<td>0.95</td>
<td>0.98</td>
<td>0.95</td>
<td>0.78</td>
<td>0.75</td>
<td>0.81</td>
</tr>
<tr>
<td><strong>Post op</strong></td>
<td>0.35</td>
<td>0.96</td>
<td>0.99</td>
<td>0.96</td>
<td>0.96</td>
<td>0.95</td>
<td>0.99</td>
<td>0.95</td>
<td>0.78</td>
<td>0.75</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**FA (WM)** – fractional anisotropy of white matter
**MD (GM)** – mean diffusivity of grey matter
**MD (WM)** – mean diffusivity of white matter
Figure 12 displays a line chart of FA of WM from before to after the operation for each patient. Three patients visibly show a marked drop in FA unlike the other test subjects who show little change. The Wilcoxon signed-rank test showed no significant difference between the FA (WM) before and after surgery (P value of 0.0859).

Figure 13 displays a line chart comparing the MD of grey matter in each patient before and after the operation. The majority of patients showed insignificant increases in MD except for one which shows an insignificant reduction. The Wilcoxon signed-rank test showed no significant difference between pre- and post-operative MD in the grey matter (P value of 0.2188).

Figure 14 displays a line chart of the MD of white matter before and after the operation for each patient. 3 patients show a mild decline whilst the remaining 5 show mild increases. The Wilcoxon signed-rank test showed no significant difference between pre- and post-operative MD WM (P value of 0.2188).

3.3 DTI Parameters from Reproducibility Studies

![Figure 15: Line charts of mean FA of WM, MD of GM and MD of WM in healthy volunteers extracted from whole brain histograms.](image)

We found the FA of WM to remain steady in 3 of the healthy volunteers. In the fourth volunteer, we observed a small reduction. The MD of white matter showed mild reductions in 3 of the volunteers and an increase in the fourth volunteer. The MD of grey matter showed a marked increase in one volunteer, a decrease in two volunteers and a small increase in one volunteer.

The means and standard deviations of the group are listed in Table 3.

<table>
<thead>
<tr>
<th>Time point</th>
<th>FA (WM)</th>
<th>MD (GM) (x10⁻³)</th>
<th>MD (WM) (x10⁻³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.3 (0.01)</td>
<td>0.83 (0.02)</td>
<td>0.74 (0.01)</td>
</tr>
<tr>
<td>2</td>
<td>0.3 (0.01)</td>
<td>0.82 (0.03)</td>
<td>0.73 (0.02)</td>
</tr>
</tbody>
</table>

Results in format: mean (standard deviation)

The mean FA of WM, MD of GM and MD of WM for the volunteers show very little to no change between the time points. The changes observed in the patients (the average change of the patients whose FA decreased= 0.081) are greater than in the volunteers (the stdev of the change in FA between timepoints = 0.003) therefore they are more likely to be due to real effects from the surgery.

3.4 Cognitive Test Score Comparison with DTI Parameters

To assess whether the changes in FA and MD correlated with the z-scores for global cognition, we created scatterplots with the differences in each DTI parameter after surgery on the x-axis versus the change in Z-scores after 3 months or 1 year on the y-axis.
Figures 16 shows scatterplots of the change in FA as a result of the surgery against the change in Z-score after 3 months from baseline and after 1 year from baseline. No visible correlation is observed.

Scatterplots are shown in Figure 17 with the change in MD after the surgical intervention and the change in Z-score after 3 months from baseline and after 1 year from baseline respectively. No visible trend is observed.

Figure 18 shows scatterplots consisting of the change in MD after surgical intervention and the change in Z-score after 3 months from baseline and after 1 year from baseline for each patient respectively. No visible trend is observed.
3.5 Fazekas’ Scale Ratings for WMHs

In order to assess the severity of white matter hyperintensities prior to surgery and their relationship with cognition, we used Fazekas’ scale. The scores obtained from the FLAIR images with Fazekas’ Scale are listed in Table 1 below. Notably, there are two patients who score high on the scale because of the formation of deep white matter hyperintensities before the operation as a result of cerebrovascular disease.

<table>
<thead>
<tr>
<th>Score</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Periventricular Lesions</td>
</tr>
<tr>
<td>AAAOP001</td>
<td>0</td>
</tr>
<tr>
<td>AAAOP002</td>
<td>3</td>
</tr>
<tr>
<td>AAAOP003</td>
<td>1</td>
</tr>
<tr>
<td>AAAOP004</td>
<td>1</td>
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<tr>
<td>AAAOP005</td>
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</tr>
<tr>
<td>AAAOP006</td>
<td>1</td>
</tr>
<tr>
<td>AAAOP009</td>
<td>0</td>
</tr>
<tr>
<td>AAAOP013</td>
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<tr>
<td>AAAOP019</td>
<td>1</td>
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<tr>
<td>AAAOP036</td>
<td>0</td>
</tr>
<tr>
<td>AAAOP037</td>
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<tr>
<td>AAAOP096</td>
<td>0</td>
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</tbody>
</table>

4. DISCUSSION

The purpose of this project was to assess the impact on cognition caused by EVAR, endovascular aortic aneurysm repair, and the correlation that change in cognition might make with fractional anisotropy (FA) and mean diffusion (MD). In our results, we found that global cognition (averaged from all subtests) significantly improved from before the operation to 3 months after the operation. No significant difference was found in our comparison of global cognition from before the operation to one year after the operation, suggesting no long-term effect of surgery on cognition. We also found no change made by the operation to the mean FA of white matter, MD of grey and MD of white matter.

4.1 Cognitive Results

These results differed from our expectations. Because of past studies, we hypothesised that there would be lower z-scores after 3 months and possibly 1 year due to post-operative cognitive dysfunction which would have occurred due to cerebral ischaemia by microemboli or cerebral oxygen desaturation (Newman et al., 2001; Slater et al., 2009; Wilson et al., 2008).

The improvement which we found in the test scores could have been a systematic product of the learning effect. Repeating similar tests may have led to score improvements due to familiarity with the material instead of cognitive improvement. We had aimed to reduce the learning effect by varying the RBANS, repeatable battery for the assessment of neuropsychological status, tests between test episodes and giving substantial periods of time between retesting (3 months and 9 months).

As suggested by Rasmussen & Siersma in 2004 the cognitive scores obtained could have also been impacted by variability. Variability is a feature known in connection with neuropsychological testing which could affect the results when repeated testing is used to detect changes in cognitive function. The factors that could impose variability can be based on the way the test is administrated or on the individual. Uncontrolled testing facilities, change of testing personnel and change of testing conditions such as the location and the time of the day can affect test scores (Rasmussen et al., 2001). Individual aspects which we cannot control include small differences in motivation or well-being between test sessions. These are multifactorial and can be related to numerous factors such as sleep, medication, anxiety etc. The anxiety and depression scale we used took this into account although we did not process its scores in calculating the z-scores.

A longitudinal study by Newman et al studied cognitive decline over a five year period in patients who underwent coronary artery bypass grafting (CABG). They found cognitive decline straight after surgery followed by a mild improvement in 6 months and then later decline after 5 years. Our study instead showed an improvement followed by a slight decline back to similar levels as at baseline. The time period used by Newman, 5 years, was longer than the 1 year we used therefore it provided greater long-term coverage. Their study, in contrast to ours, measured cognitive scores at discharge. Our study, if we had measured cognitive scores as early as within a few days after the operation, may have found a different impact on cognition made by the procedure. The three months waited for retesting may have been long enough to cause the change in scores that we observed.

In our results, some patients improved after the operation and there were some who declined.
The differences in outcomes suggest individual confounding factors which influenced post-operative cognitive function. Age, extent of cerebrovascular disease, hypertension and low education levels can influence the chances of POCD: post-operative cognitive decline (Tan & Amoako, 2013). In this study, we only took note of the age of the patients because it is the greatest risk factor and can be linked to the other factors. Age is thought to be a major factor due to changes in vasculature and autoregulation of cerebral blood flow in the elderly (Martin, Melo, & Sousa, 2008). In this study, we ensured that we controlled for the variable of age, to an extent, by admitting only those between 64 and 79 years of age as test subjects.

It is possible that we could have found a stronger correlation if we had analysed specific domains such as executive functioning and processing speed like some studies (Jokinen, 2005; Lawrence et al., 2013).

### 4.2 Fazekas’ Scale

Another hypothesis due to past research that we made for this study was that the patients who scored high on Fazekas’ scale (more WMHs) for their pre-operative FLAIR images were more likely to have global cognitive decline (Benedictus et al., 2015; Jokinen, 2005). A high score on Fazekas’ scale denotes the presence of extensive white matter lesions. We expected the presence of white matter lesions in varying degrees in the patients before the operation as a result of hypertension (Liao et al., 1996) which is common in aneurysm patients (Spittell, 1983).

Four patients scored 0s on the scale for periventricular and white matter lesions on Fazekas’ scale and 2 patients (‘2’ and ‘37’ from table 4) scored highly on the scale. Contrary to our hypothesis, both showed improvements in their cognitive scores 3 months and 1 year post-operation. This difference may have been due to the location of the white matter lesions. Smith et al. in 2011 found specific loci of white matter lesions to be closely associated with executive function and episodic memory. For executive function, WMH clusters found in bilateral inferior frontal white matter, bilateral temporal-occipital and right parietal periventricular white matter were found to be associated with decline. For episodic memory, clusters in the bilateral temporal-occipital and right parietal periventricular white matter were associated with decline. In both patients, we found that these regions were not severely impacted by the WMH lesions.

### 4.3 DTI Measures

We originally decided to use DTI parameters for this project because they would provide sensitive measures of brain damage after the surgery (Della Nave et al., 2007). DTI parameters provide whole brain measures which can show global changes instead of the local changes which would be observed via DWI images. In line with past research on leukoaraiosis, we expected a decline in cognition after EVAR to correlate with a reduction in FA and an increase in MD (Della Nave et al., 2007). In our study, for the whole group, there was no difference between the whole brain DTI measures which were the FA of white matter, MD of grey matter and MD of white matter pre-operation and post-operation. It is possible that for our findings, the operation procedure may have been safe enough to cause little to no neuronal damage and cellular oedema which would have kept FA and MD stable and resulted in no cognitive deficits. Also, it is likely that our patient numbers were too small and our patient demographics were not tight enough to see a significant change in whole brain FA and MD.

Individually, three patients (‘1, 3 and 5’), on Figure 12, had visible declines in the FA of their white matter. Unexpectedly, two of them showed mild improvements in their cognitive scores (‘3’ and ‘5’), whilst the other showed the expected mild decline within 3 months followed by a small improvement after a year.

Figures 13 and 14 show only small, insignificant changes in MD before and after the operation for each patient.

We created scatterplots to compare the changes in z-scores and the DTI measures. Figures 16-18 display no visible trend between cognition and MD or FA. It is likely that the small number used in this study caused our inability to correlate these two factors.

### 4.4 Limitations

The low number of patients (cognitive scores from 12 test subjects and DTI measures from 8 due to missing data) used in this study was a limitation. A larger sample would have increased our chances of finding significant differences in the pre and post-operative data because it would more reliably reflect the population.

Another drawback of having a small sample was that we were limited on how we can analyse
the psychometric test data. In this study, we created a composite score, the z-score, for the global cognition of patients before and after the surgery. It is possible that surgery will have had a different effect on certain domains of cognition in comparison to others. Unfortunately, we did not have enough patient data to enable a subtest analysis which would give reliable results. Charlton et al found MD and FA to relate with executive function, working memory and processing speed. It is possible that with a larger sample we would have found reduction in subtest scores relating to the aforementioned domains if we had individually tested for them.

We were also unable to confirm microembolisation from the operation because we deliberately did not assess the DWI images obtained. Emboli events occurring in cardiac surgery are visualised on DWI as new small ischaemic lesions (Knipp et al., 2005). If we assessed the DWI images, we will have had a confirmed physiological reason for cognitive decline. Without the recognition of apparent ischemic lesions on DWI, one can assume from our results that the EVAR procedure was performed safely enough that no adverse neurocognitive changes occurred in the patients.

4.5 Conclusion

These results have suggested, against past evidence (Funder et al., 2009; Gao et al., 2005) that post-operative cognitive dysfunction is not a definite outcome of cardiac surgery. For further investigation, I would suggest a repeat of this experiment with more patients and longer time periods for cognitive testing. Also, I would suggest further research concerning why patients have different cognitive outcomes following surgery. Independent investigation with the control of demographic factors such as years in education, type of occupation, retirement age and family history of decline may show concrete evidence of risk factors to POCD. Improved awareness of individual risk can lead to better informed decisions for borderline patients (with AAAs just below 5.5cm in diameter). Another possible further investigation suggested in this field would be region of interest (ROI) analysis in lesions and normal appearing white matter in order to find subtle DTI differences which impact cognition.

In conclusion, the results of this study have shown in this small patient group that EVAR causes no change in the DTI parameters investigated (FA of white matter, MD of grey matter and MD of white matter). We also found a slight improvement to cognition 3 months after the surgery and no longer term difference after 1 year. In addition, patients with extensive white matter hyperintensities were not necessarily predisposed to greater cognitive decline as we had expected.

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http://doi.org/10.1093/icvts/ivs317


http://doi.org/10.1161/CIRCULATIONAHA.108.837807


