Glioblastoma blood flow measured with stable xenon CT indicates tumor necrosis, vascularity, and brain invasion

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Tumor vasculature is a promising therapeutic target in glioblastoma. Imaging tumor blood flow may help assess the efficacy of anti-angiogenic treatments. We determined the clinical usefulness of stable xenon CT performed preoperatively in patients with glioblastoma. This is a prospective cohort study. We determined absolute tumor blood flow before surgery in 38 patients with glioblastoma using stable xenon CT. We also histologically examined tumor specimens obtained from surgery and quantified their vascularity (by CD31 and CD105 immunostain), necrosis (by hematoxylin and eosin stain), and the presence of neuronal processes (by neurofilament immunostain). According to the xenon CT blood flow map, there are 3 types of glioblastoma. Type I glioblastomas have unimodal high blood flow histograms; histologically there is little necrosis and vascular proliferation. Type II glioblastomas have unimodal low blood flow histograms; histologically there is prominent necrosis and vascular proliferation. We propose that in type II glioblastoma, the abnormal vessels induced by hypoxia are inefficient at promoting blood flow. Type III glioblastomas have multimodal blood flow histograms. Histologically there is significant neuronal tissue within the tumor. Patients with type III glioblastomas were more likely to develop a post-surgical deficit, consistent with the inclusion of normal tissue within the tumor. Preoperative measurement of absolute blood flow with stable xenon CT in patients with glioblastoma predicts key biological features of the tumor and may aid surgical planning.

Keywords: cerebral blood flow, glioblastoma, microvessel density, necrosis, xenon CT.

Glioblastoma multiforme (GBM) encompasses a heterogeneous group of aggressive brain tumors with characteristic histological features of vascular proliferation and necrosis.1,2 There is substantial experimental evidence3,4 that angiogenesis is essential for the proliferation, infiltration, and survival of GBM cells. Recent clinical data5,6 also indicate that inhibiting angiogenic pathways slows GBM growth. Necrosis is central to glioblastoma biology and is implicated in vascular proliferation and hypoxic regulation of tumor invasion and response to treatment. GBM heterogeneity, which arises from genetic variations among individual tumors,7,8 has important clinical implications because it produces a large variability in the rate of GBM growth, infiltration, response to treatment, and patient survival.9–11 Therefore, subclassifying GBM would improve prognostication and therapeutic response.

Currently, MR imaging is the investigation of choice for planning surgery and monitoring response to treatment. However, routine MR sequences do not provide information on GBM vasculature. Given the importance of angiogenesis in determining the biological behavior of GBM,3,4 we obtained absolute blood flow (BF) maps preoperatively in 38 patients with GBM. We investigated whether BF maps provided clinically useful information not available from ordinary imaging, including tumor vascularity, necrosis, and infiltration into the surrounding brain.
There are many techniques available for measuring cerebral BF, including dynamic contrast enhanced (DCE)–MR, PET, arterial spin labeled MR, and stable xenon CT (XeCT). DCE–MR measures the transit time from an input artery to the cerebral circulation and may therefore be inaccurate when anatomical distortion is present and when the region of interest (ROI) crosses vascular territories. The MR perfusion parameter for BF is the mean transit time (MTT), with prolonged MTT indicating reduced BF. MTT is potentially unreliable due to the assumptions made in the context of tumors. Other markers of tumor vascularity include cerebral blood volume and the contrast leakage coefficient, which are highly valuable and may predict response to treatment and survival. PET uses radiolabeled tracers and derives tissue metabolism or BF according to the time course of radiation emission. Although the spatial resolution of PET has improved, it is challenging to use in acutely ill patients due to the short radioisotope half-lives. Arterial spin labeled MR uses magnetically labeled protons as the diffusible tracer and is inaccurate where normal anatomy is lost or where the input artery cannot easily be defined. PET and DCE–MR measure BF in various disease states and healthy subjects. Although the spatial resolution of PET has improved, it is challenging to use in acutely ill patients due to the short radioisotope half-lives. Arterial spin labeled MR uses magnetically labeled protons as the diffusible tracer and is inaccurate where normal anatomy is lost or where the input artery cannot easily be defined. PET and DCE–MR measure BF in various disease states and healthy subjects. Although the spatial resolution of PET has improved, it is challenging to use in acutely ill patients due to the short radioisotope half-lives. Arterial spin labeled MR uses magnetically labeled protons as the diffusible tracer and is inaccurate where normal anatomy is lost or where the input artery cannot easily be defined. PET and DCE–MR measure BF in various disease states and healthy subjects. Although the spatial resolution of PET has improved, it is challenging to use in acutely ill patients due to the short radioisotope half-lives. Arterial spin labeled MR uses magnetically labeled protons as the diffusible tracer and is inaccurate where normal anatomy is lost or where the input artery cannot easily be defined. PET and DCE–MR measure BF in various disease states and healthy subjects.

Studies of GBM BF have therefore used different markers of vascularity, but no study has ever examined absolute BF in GBM. Here we used XeCT, which offers the advantages of high (approximately 1.5 mm in-plane) spatial resolution and the ability to measure absolute BF values without the need to define an input artery to the ROI. XeCT uses nonradioactive $^{131}$Xe as a soluble, nonmetabolized, x-ray attenuating tracer that accumulates within tissues according to the partition coefficient (ie, solubility of Xe within the tissue) and to the rate of Xe delivery (ie, tissue BF). At each timepoint, the Xe concentration within the tissue is determined from the increase in Hounsfield units and in the arterial Xe concentration from the end-tidal Xe. These factors are related by the Kety–Schmidt equation, which allows the BF and partition coefficient to be derived for each voxel. Xe diffuses freely across both an intact and a disrupted blood–brain barrier, and thus XeCT can be used to measure absolute BF in various disease states and healthy subjects. XeCT has been used extensively in subarachnoid hemorrhage to differentiate ischemic, but salvageable, brain tissue from irreversibly infarcted tissue. Three studies used XeCT in patients with glioma to predict tumor grade from the xenon tissue partition coefficient, but no analysis of the different patterns of tumor BF was undertaken. There was also no attempt to correlate differences in BF with histological features. We examined GBM tissue and correlated key histological features with the pattern of BF obtained from XeCT.

**Materials and Methods**

**Patients**

Adult patients presenting to the Department of Neurosurgery, St. George’s Hospital, London, with radiologically presumed (and subsequently histologically confirmed) GBM between August 2008 and October 2009 were prospectively recruited. Ethical approval was from the Wandsworth Local Research Ethics Committee. All patients gave informed written consent. Confused or comatose patients were excluded.

**Patient Demographics**

Forty patients were recruited and 2 excluded, one due to motion artifact and one due to incomplete tumor coverage by the scan. Of the 38 patients included, 11 were female and 27 male. Sufficient tissue for pathological study was available for 37, of which 3 had stereotactic biopsy and 34 had craniotomy and debulking. One patient had an anterior midline tumor involving the corpus callosum, preventing analysis of the contralateral region. Median age was 64 years, and the median KPS was 80. Twelve patients had biopsy and 26 had volume-reduction surgery (debulking or gross total resection). Thirty-seven patients died, and 1 was lost to follow-up at 1 month. Overall median survival was 225 days.

**Blood Flow Measurement**

Thirty-eight subjects had a xenon CT scan before surgery for biopsy or debulking. Scans were performed on a Lightspeed 16-slice CT scanner (General Electric) using a standard 6-level XeCT protocol with 10-mm slice thickness, 1.5-mm in-plane resolution, and a Xenon Enhancer 3000 delivery system (Diversified Diagnostic Products [DDPi]). A 28% Xe, 40% O$_2$, 4.5-min wash-in protocol was used. Images from DICOM (Digital Imaging and Communications in Medicine) were transferred to a personal computer (Dell) and initially processed with XeCT system software version 1.0 (DDPi) using the xenon indicator wash-in curve to provide an absolute BF map. The subject’s hematocrit value was used in the BF calculation. Images with artifact from failure to reach equilibrium at 28% end-tidal xenon during the 4.5-min study or with motion artifact were excluded. Studies in which the 6 levels of the CT scan did not cover the whole tumor volume of interest (VOI) according to the diagnostic imaging were also excluded.

**Cerebral Blood Flow Software**

We found that the old software (XeCT v1.0) was inadequate for evaluation of tumor BF. A novel software for analysis of the BF maps was devised and written by S.T., M.C., and R.Z. This imports data from the XeCT system software and allows multiple 2D ROIs on consecutive slices of the BF map to be defined separately and combined to produce a 3D VOI. The midline of the brain was used to define a mirror image of the contralateral hemisphere. The ROIs that make up this contralateral VOI were inspected to confirm that anatomical distortion or midline shift had not caused
inclusion of inappropriate structures such as bone or CSF spaces. ROI values were compared against the same ROIs defined using XeCT v1.0 to confirm reliability of the new software. We determined the error of manual tumor definition by repeating the measurements of 10 tumors and 10 normal ROIs using 5 observers.

**GBM Blood Flow**

ROIs were defined freehand on the BF map, with reference to the subject’s diagnostic structural imaging (contrast-enhanced CT or MR). The tumor was considered to be the volume of T1 contrast enhancement on MR or the CT contrast enhancement. Areas of tumor with questionable contrast enhancement were included if they showed marked signal abnormality in fluid attenuation inversion recovery (FLAIR). The data for all VOIs were exported to Excel 2008 (Microsoft) for further analysis. For analysis of radiological-pathological agreement, we excluded cystic areas of the tumors (as cyst fluid would be absent from the tissue samples). VOIs were defined within the cystic areas of 6 tumors with radiologically and surgically confirmed cystic components. The BF values of all cystic areas studied had a median of 4.2 mL/100 g/min. For this part of the study we therefore excluded pixels with BF < 5 mL/100 g/min from all the tumor VOIs, regardless of whether a cystic component was suspected radiologically or not, leaving a tumor VOI composed radiologically of contrast enhancing tissue or solid tissue within a volume of contrast enhancement.

**Cluster Analysis**

We derived the following parameters from the GBM BF map: mean baseline attenuation; mean BF; standard deviation of BF; ratio between BF of the VOI of the normal mirror-image side to the GBM BF; percent GBM with BF >20 mL/100 g/min; and kurtosis and skewness of BF histogram. We did Pearson similarity cluster analysis to see if the GBMs fall into distinct groups based on these BF parameters.

**Tissue Processing**

GBM tissue obtained during surgery was fixed in formalin and processed into paraffin. Where debulking surgery was performed, tissue samples from throughout the surgical field were used to ensure adequate representation of the tumor. Tissue sections were stained with hematoxylin and eosin (H&E) or immunostained for the vascular endothelial marker CD105 and PCAM-1 (Dako) 1:40 or for neurofilament (Dako) 1:400, followed by the appropriate biotinylated secondary antibody (Vector Labs) and avidin-horseradish peroxidase. Immunoreactivity was visualized brown with 3,3’-diaminobenzidine /H2O2, and sections were counterstained with hematoxylin and examined using a Zeiss Axiom digital microscope system. Subjective scores were averaged between two observers (M.C., L.B.).

**Necrosis**

Stained tissue sections were photographed at low power. Necrosis was graded from the H&E sections as 0 = no necrosis, 1 = incipient necrosis or few areas of pseudopalisading necrosis, 2 = multiple nonconfluent areas of necrosis obvious at low power, 3 = confluent areas of necrosis but less than 50% of area covered, and 4 = more than 50% necrosis. Five random fields per tissue were scored to give a total of 20 per case.

**Vascularity**

Staining for the vascular endothelial marker CD105 was scored by an automated color deconvolution and thresholding process as previously described, which counts the overall percent immunopositivity for each marker, normalized for tumor area per field. We scored CD31 immunostain in the same way to confirm the CD105 findings.

**Neurofilament**

Immunostaining was scored on a scale of 1 to 5 in 5 different regions of GBM. We scored the extent of staining (1 = no positive stain, 2 = occasional positive stain in less than 2% of area, 3 = positive stain throughout but less than 50%, 4 = positive stain in more than 50% of the tumor but some areas not stained, 5 = positive staining throughout). We also scored GBMs for the pattern of staining compared with a normal human brain positive control (1 = dots of positivity in nonlinear pattern or no stain, 2 = some dots arranged in lines but mostly nonlinear, 3 = dots mostly in lines, 4 = dots with some intact neuronal processes, 5 = mostly or all intact neuronal processes). Thus the overall score for positivity and staining pattern ranged from 5 to 25.

**Statistics**

Data were analyzed using Microsoft Excel 2008 and XLStat v6.1 (Addinsoft). Correlation between data sets was measured using Pearson’s coefficient. Nonparametric data were analyzed with a Kruskal–Wallis test for multiple pairwise comparisons and a Mann–Whitney test with Bonferroni correction for post hoc paired comparisons. Unsupervised cluster analysis was done according to Pearson similarity.

**Results**

**Evaluation of the New Software**

All studies were initially processed using XeCT v1.0 and then using the novel BF visualization software. We validated the data in 2 ways. First, a single observer defined
freehand a 2D BF ROI for 10 GBMs in XeCT v1.0. This was repeated 5 times. Coefficient of variation for the repeated measurements of tumor area, baseline attenuation, tumor BF, tissue partition coefficient, and confidence across these 10 ROIs was 4.4% (2.2%–6.6%). Second, 2 observers (M.C. and a senior neurosurgeon) independently defined freehand a 2D BF ROI for 20 GBMs in XeCT v1.0 and then in the new software. All parameters of the ROIs (area, tumor BF, partition coefficient, and confidence) correlated well across these 20 ROIs with R > 0.99. This shows that our method of defining the tumor does not have significant error and that the new software is a reliable visualization platform that does not introduce error. We therefore used the new software to define the tumors as VOIs by comparison with MR or CT. Ten repeat measurements by independent observers revealed a low coefficient of variation (2%–8%, depending on the BF parameter). We studied the whole tumor and contralateral mirror-image ROI for comparison. BF < 5 mL/100 g/min accounts for approximately 25% of voxels for the 6 tumors with a major cystic component, but less than 10% of voxels for the remaining tumors.

Patterns of Blood Flow in GBM

The histograms of the 38 BF maps fell into 3 distinct groups. The first group (type I, 8 patients) had BF values distributed around a central peak (Fig. 1A). The second group (type II, 22 patients) had BF values peaking at a low BF, suggestive of necrotic tumors (Fig. 1B). The third group (type III, 8 patients) had 2 or more BF peaks (Fig. 1C).

Necrosis in GBMs

We hypothesized that low overall GBM BF (as seen in type II histograms) indicates large regions of tissue necrosis, with high BF indicating little necrosis. To test this hypothesis, we plotted the mean GBM BF obtained from the XeCT BF histogram versus necrosis as determined histologically (Fig. 2). There was a negative correlation (R = −0.54, P < .01), suggesting that low overall GBM BF indicates more extensive necrosis. This negative correlation remained significant regardless of the BF parameter studied: markers of high BF (proportion of tumor with BF > 20 mL/100 g/min) were also negatively correlated with necrosis.

Vascularity in GBMs

Given the angiogenic nature of GBM, we hypothesized that tumors with high BF have increased vascularity. We computed the proportion of the tumor with BF > 20 mL/100 g/min in the expectation that this would positively correlate with high tumor vascularity. Vascularity was taken as percent CD105 (endothelial) immunopositivity within the tumor. Unexpectedly, we found a negative correlation between vascularity, as measured by CD105 positivity, and the proportion of the tumor with BF > 20 mL/100 g/min (R = 0.48, P < .01) (Fig. 3). This negative correlation still holds if a BF of greater than 15, 25, 30, or 40 (rather than 20) is taken as the cutoff (not shown) or if CD31 immunostaining is used instead of CD105 (R = 0.44, P < .01). These findings are consistent with tissue ischemia driving the formation of many abnormal vessels (ie, increased necrosis causes increased angiogenesis).

Neuronal Fibers in GBMs

We hypothesized that the multimodal GBM BF histogram (type III) arises because of the coexistence of different tissue types within the tumor, such as a combination of tumor cells and normal brain. We therefore immunostained GBM tissue for neurofilaments, looking for neuronal processes within the tumor. GBM samples from 18 patients were used, for whom adequate tissue was available. Three patterns of neurofilament immunoreactivity were seen. Pattern 1 had little or no neurofilament immunoreactivity and was associated with type I BF histograms. In pattern 2, neurofilament positivity was arranged as dots, indicating degenerating neuronal processes. Pattern 2 was associated with type II BF histograms (tumor necrosis). Pattern 3 was a normal immunostaining pattern similar to that seen in normal brain tissue, indicating the incorporation of normal brain tissue within the tumor. Pattern 3 was associated with multimodal (type III) BF histograms. Fig. 4A shows examples of the 3 patterns of neurofilament immunostaining within GBMs, and Fig. 4B shows significant differences in the extent of neurofilament positivity between types II and III histogram tumors and in the tumor with BF > 20 mL/100 g/min. These differences are consistent with the hypothesis that there are differences in the extent of neurofilament positivity between types II and III histogram tumors and in the tumor with BF > 20 mL/100 g/min.
the pattern of neurofilament staining between all types of tumors. Since type III BF histograms indicate intact neurons within GBM, we asked whether debulking type III tumors is more likely to produce a neurological deficit than debulking type I or type II tumors. No patient (7/7) with a type I or type II GBM BF histogram who had had debulking surgery had a surgically induced neurological deficit; 5 of these patients had surgery in an eloquent area of the brain. However, 3/6 patients with a type III GBM BF histogram had a new, surgically induced neurological deficit: speech disturbance or limb weakness; 4 of these patients had surgery in an eloquent area of the brain. The neurological deficit was unrelated to tumor size or the extent of tumor spread; there was no significant difference between GBMs with types I, II, and III BF histograms in tumor size (defined as the area of contrast enhancement on T1) or tumor spread (defined as area of FLAIR signal change/area of T1 contrast enhancement).

Subgroups of GBM

Unsupervised cluster analysis divided the tumors into 2 distinct groups, 1 and 2, according to their BF parameters (Fig. 5). There were significant differences between the groups in most of the BF parameters: xenon tissue partition coefficient; mean BF and tissue homogeneity of BF; ratio of tumor to contralateral side BF; hyperperfusion fraction; and kurtosis and skewness of the BF map (Table 1), confirming that the 2 groups were well-separated by their BF parameters. There were also significant histological differences between the 2 GBM groups with CD105 positivity, CD31 positivity, and necrosis significantly higher in group 2 versus group 1. Kaplan–Meier analysis showed no significant survival difference between the 2 groups. Tumor clusters were unchanged when analysis was done with versus without the cystic regions.

Discussion

We showed that the GBM BF map gives information about key biological features of the tumor, such as necrosis and vascularity, as well as the interaction between the tumor and the brain. These features are involved in the response and resistance to anticancer therapy. We also found an association between the pattern of tumor BF and the presence of neuronal tissue within the tumor. This has
clinical relevance for the maximal safe resection of GBM, the survival benefit of which is well-documented.31,32

XeCT allowed us to quantify tumor necrosis. There is a well-characterized association between hypoxia in GBM and the molecular phenotype of the tumor, primarily mediated by hypoxia inducible factor–1.33,34 Changes in the necrotic elements of GBM are implicated in escape from anti-angiogenic therapy,6,29,30 and therefore the ability to visualize necrotic changes at the start and during a patient’s anti-angiogenic treatment could be clinically valuable.

XeCT also allowed us to quantify tumor vascularity. Angiogenesis is a major target for novel GBM treatments1,4,26,33 Biomarkers of tumor vascularity are therefore important as endpoints in clinical trials of novel anti-angiogenic agents and as monitors of response to treatment. The “glomeruloid” vessels in GBM do not function in the same way as normal brain vessels. Glomeruloid vessels have high capillary permeability and provide inadequate tissue perfusion.5,35 This may explain our observation that reduced tumor BF is a marker of increased tumor vascularity.

Table 1. BF map and histological parameters (mean ± SEM) for the 2 GBM groups (1 and 2) identified by cluster analysis

<table>
<thead>
<tr>
<th>BF Map Parameter</th>
<th>Group 1</th>
<th>Group 2</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline CT attenuation (HU)</td>
<td>32 ± 1.3</td>
<td>31 ± 1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Mean tumor BF (mL/100 g/min)</td>
<td>45 ± 3.6</td>
<td>23 ± 1.5</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Tumor BF standard deviation</td>
<td>25 ± 1.7</td>
<td>18 ± 1.0</td>
<td>&lt;.005</td>
</tr>
<tr>
<td>Partition coefficient (lambda)</td>
<td>1.0 ± 0.02</td>
<td>0.94 ± 0.028</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Ratio tumor BF : normal BF</td>
<td>1.3 ± 0.14</td>
<td>0.72 ± 0.048</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Hyperperfusion fraction</td>
<td>0.76 ± 0.038</td>
<td>0.46 ± 0.039</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>BF histogram kurtosis</td>
<td>−0.35 ± 0.11</td>
<td>1.6 ± 0.44</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>BF histogram skewness</td>
<td>0.42 ± 0.10</td>
<td>1.3 ± 0.11</td>
<td>&lt;.0005</td>
</tr>
<tr>
<td>Histology parameter</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD31 positivity (%) area</td>
<td>3.2 ± 0.42</td>
<td>4.7 ± 0.67</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>CD105 positivity (%) area</td>
<td>3.5 ± 0.38</td>
<td>5.3 ± 0.70</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Necrosis (/20)</td>
<td>11.7 ± 0.96</td>
<td>14.4 ± 0.68</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>

Abbreviations: HU, Hounsfield units; NS, not significant.

Hyperperfusion fraction = part of tumor with BF > 20 mL/100 g/min.
(MTT, cerebral blood volume, and contrast leakage coefficient) also related to tumor vascularity. In our view, these MR parameters are difficult to interpret because they do not measure GBM BF directly and are confounded by several factors.

XeCT also provides information about GBM brain invasion. The prognostic importance of the extent of surgical resection in GBM is well-recognized, and gross total resection of the T1 enhancing volume of the tumor without incurring neurological deficit is the aim of surgery where possible. We discovered an association between the BF patterns of GBMs and their incorporation of neural elements. Patients with a low BF had few neurofilaments as well as abnormal neurofilament staining, indicating neuronal necrosis. The neurological deficit associated with such tumors is unlikely to be exacerbated by aggressive resection. Multimodal BF histograms were associated with incorporation of normal-looking neural tissue within the GBM. Aggressive resection of such tumors has a high risk of causing neurological deficit. The preoperative XeCT scan may thus enhance the safety of surgical resection. Should aggressive surgery be planned for such patients, the risk of neurological deficit might be minimized by awake craniotomy with intraoperative neurological assessment.

Our study has some limitations. As with other clinical studies of GBM that rely on histological sampling, it is difficult to relate accurately the location of the tumor specimen with the preoperative imaging. Another limitation is the inability to coregister the XeCT scans with the conventional preoperative imaging to enable thresholding and automatic segmentation of the tumor ROIs. As explained in detail in the Methods section, several measures were taken to reduce these errors. Some of the limitations are inherent to the heterogeneity of GBMs. Cluster analysis revealed 2 distinct groups of GBM with markedly different BF characteristics. Although there was no significant survival difference between the 2 clusters, this finding raises several intriguing hypotheses, which can easily be tested in future studies. First, the 2 GBM clusters may respond differently to anti-angiogenic chemotherapy, and therefore XeCT performed at presentation could be used to predict response to anti-angiogenic treatment. Second, longitudinal changes in the BF histogram of individual patients might predict response to treatment or even tumor recurrence. Third, a XeCT study in patients with low-grade gliomas, who are managed conservatively, might reveal changes in BF histograms that precede tumor progression or a cluster of BF histograms that predict a more benign course. One way to address these hypotheses is to perform XeCT in GBM patients recruited in other clinical trials, such as trials of anti-angiogenic chemotherapy.

We conclude that preoperative XeCT in patients with GBM provides information about basic tumor characteristics, including necrosis, vascularity, and brain invasion. This information may be useful when planning the extent of surgical resection.

Acknowledgments

Funded by grants from The Neurosciences Research Foundation, London Deanery, and St. George’s Hospital to M.C. and M.C.P. CRUK grants C13468/A6718 and C309/A8274 to A.J. and C.J.

Conflict of interest statement. None declared.

Funding

M.C. is funded by The London Deanery, The Neurosciences Research Foundation, and St George’s Hospital Charitable Trust.

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