Index of Changes

Examiner 1

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Suggested changes:

1. There are different methods to assess the penumbra or “mismatch” in acute ischemic stroke: some are pure imaging-based mismatch—used in quite a lot of trials or in clinical practice; some are imaging-clinical deficit mismatch—such as in the recent DAWN trial. What are the main advantages and disadvantages of imaging-based mismatch and imaging-clinical mismatch, in view of the clinical relevance and generalizability in clinical practice or research?

2. You described quite a few imaging-based methods for penumbra quantification in the literature review—why did you use the PWI-DWI mismatch pattern in your studies? Any particular advantage of this pattern over others?

Response / Changes:

To highlight the recommended discussion, I have cooperated additional paragraphs within chapter 2.4 which is indicated by italic and bold. The rest is original text from the PhD thesis.

2.4 Other methods for the assessment of the Ischemic Penumbra

The author’s four publications in this thesis are based upon the PWI/DWI mismatch model. The author chose this method initially because CT perfusion was simply not widely available at the time and the core threshold was far from certain or validated. The DWI has been labelled as the gold standard for infarct core identification. As mentioned earlier the ADC threshold has been validated against final infarct volume in non-reperfusion
model. The series of DEFUSE studies (DEFUSE 1, 2 and 3) are the best examples of the validation of the MRI PWI/DWI mismatch.\textsuperscript{147, 289, 297, 298} This series of studies unquestionably demonstrated that only patients with target mismatch would respond to reperfusion therapy. A large PWI/DWI mismatch might also indicate the presence of large vessel atherosclerotic lesions.\textsuperscript{299} Since time is brain rapid triage of patient with acute ischemic stroke in emergency department is crucial. PWI/DWI mismatch was shown to have 95.9% sensitivity and 98.4% specific for accurate large vessel occlusion triage for endovascular clot retrieval.\textsuperscript{300}

Accurate identification of the target mismatch is the key to good clinical outcome. One of the most validated penumbral perfusion threshold is Tmax more than 6 seconds delay relative to the contralateral hemisphere and this threshold was further validated using $^{15}$O2 water PET study.\textsuperscript{143}

CT perfusion is currently the most widely used perfusion imaging modality globally. This is due to its wide availability, less contraindication issue (such as metal contraindication for MRI), less prone to motion artefact and less restricted by weight issue. Another concern with MRI is the time delay. Alber et al studied the data from SWIFT PRIME and reported that patient who were randomised by MRI had longer door to randomisation time compare to CT perfusion but such delay did not translate into poorer clinical outcome.\textsuperscript{17}

One of the potential benefit of DWI over CT perfusion core (either CBF or CBV) is the identification of small subcortical and lacunar lesions. The development of whole brain CT perfusion seems promising in the identification of these lesions.\textsuperscript{301}

2.4.1 The MRA/DWI Mismatch

Endovascular clot retrieval (ECR) has permanently changed the stroke therapy paradigm given its extremely powerful treatment effect. Hence the focus in the assessment of acute stroke patient is not just about finding the target match but also to identify the large vessel
occlusion which requires immediate recanalization. The concept of MRA/DWI mismatch is the presence of large vessel collusion on MRA (internal carotid artery or middle cerebral artery M1 or proximal M2) with a relative small DWI lesion (usually less than 25ml in volume). This simply reflects the presence of a large penumbra without demonstrating it radiologically. This was first described in 2008 and patients with MRA/DWI mismatch had better clinical outcome compared to patients without the mismatch after recanalization.\textsuperscript{302} This finding was further validated by Deguchi et al.\textsuperscript{303}

This approach has been put forward as a simpler version of the blood flow/tissue dysfunction relationship. Time of flight MRA uses flowing blood as source of contrast. The advantage of time of flight MRA is it does not require intravenous contrast. It can depict occlusion of the major arteries of the circle of Willis down to second and third order branches of the MCA. Arterial occlusion is used as a surrogate for perfusion deficit. An example was given by Lansberg et al who studied patients from Diffusion Weighted Imaging Evaluation for Understanding Stroke Evolution Study (DEFUSE) in which patients who received intravenous tPA where studied with MR to better define MR DWI/PWI and MRA relationships\textsuperscript{304}. Patients with MRA/DWI mismatch were more likely to benefit from reperfusion with tPA and had better clinical outcomes compared to patients without MRA/DWI mismatch.\textsuperscript{304} In a follow study from the same group using data from DEFUSE 2 and studied the function outcome of a cohort of patients defined by MRA-DWI mismatch (internal carotid artery or middle cerebral artery (M1) occlusion with DWI core volume < 50ml). Patients with MRA-DWI mismatch showed improved functional outcome at 3 months compared to patients without MRA-DWI mismatch.\textsuperscript{195} Desmoteplase in Acute Stroke 2 (DIA2) trial\textsuperscript{305} showed that patients with a mismatch and large vessel occlusion on MRA or CTA was associated with less favorable clinical outcome compared to patients without large vessel occlusion. This finding was replicated in several studies.\textsuperscript{303,306} A caveat with this approach is that it cannot assess for volume of salvageable tissue but an assumption of the existence of the penumbra.

\textbf{2.4.2 The Clinical/Imaging Mismatch}
Researchers and clinicians have identified acute stroke patients with severe clinical deficits with relatively small DWI lesions on MRI; this has been termed clinical-diffusion mismatch. The clinical deficit is due to a presumably large region of ischemic penumbral tissue which is not visualized and the relatively small volume of DWI further suggests the potential for salvage of the tissue. It was proposed that the clinical stroke severity, such as National Institute of Health Stroke Scale (NIHSS) would relate directly to the extent of the PWI which incorporated both the penumbra and the infarct core.

*The clinical/DWI mismatch is generally based on the concept that if the clinical signs (NIHSS > 8) are more severe than the size of the infarct core (DWI < 25ml) then there must a substantial amount of penumbra yet to be salvages.* Clinical /DWI mismatch avoids the need for perfusion imaging which can avoid the issue of renal impairment and radiation exposure. The earlier model utilised CT ASPECT score which did not show to accurately identify the cohort of acute stroke patients who would respond to reperfusion therapy. This was likely to due to poor sensitivity of ASPECT CT in the identification of core. Using CBV or DWI to identify the core, clinical/DWI mismatch has been shown to be able to identify patients who will respond to reperfusion therapy. Unsurprisingly using the same cohort of patients PWI/DWI mismatch was superior to clinical/DWI mismatch in selecting patients who will respond to reperfusion therapy within 3-6 hours from stroke onset. Additional MRA information on large vessel occlusion can improve the power of clinical-DWI mismatch.

Prosser et al studied 79 patients with acute ischemic stroke and defined clinical/DWI mismatch as NIHSS less or equal to 8 and DWI lesion less than or equal to 25 ml. They found that the clinical/DWI mismatch had a 93% specificity but only a 53% sensitivity in detecting a PWI/DWI mismatch. Lansberg et al compared clinical/DWI mismatch to PWI/DWI mismatch and reported that the presence of PWI/DWI mismatch was correlated with a favorable outcome after reperfusion but same was not found in patients with clinical/DWI mismatch. Conversely, Choi et al used CT rather than MRI to study the clinical/imaging mismatch and found that the presence of clinical/CT mismatch did not predict a response to tPA within 3 hours of stroke onset. Messe et al compared CT/clinical mismatch to PWI/DWI mismatch and found that the former did not correlate with the latter. Kent et al
studied the correlation of clinical/CT ASPECT (Albert Stroke Program Early CT Score) score mismatch with respond to thrombolytic therapy and reported the CT/ASPECT score did not reliably identify patient who would response favorably to thrombolytic therapy. From these studies it can be concluded that clinic/imaging mismatch may provide an indicator of the presence of salvageable tissue but this is not as accurate as PWI/DWI mismatch especially if non-contrast CT is used and the imaging modality.

The DAWN (DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention with Trevo) study examined the hypothesis of reperfusion therapy up to 24 hours from stroke onset via thrombectomy reported improved clinical outcome in patients with successful reperfusion. The study employed a complex clinical (NIHSS and age) -core (DWI or CT perfusion core) volume selection criteria. The success of this study has provided further validation of the clinical-core mismatch method.

### 2.4.3 FLAIR/DWI Mismatch

The presence of normal or high T₂ contrast and low ADC values may be associated with either progression to necrosis or salvaged of the ischemic tissue. The FLAIR/DWI mismatch is based on the delay signal appearance on T2 weighted sequences such as FLAIR. Dynamic MR perfusion images requires contrast agent, power injector and post-processing. By contrast FLAIR sequence is routinely acquire in stroke MR protocol. Hyperintensity on FLAIR images can be assessed visually and without the need for complex post-processing. The hyperintense signal on FLAIR images may signify irreversible cerebral tissue damage. As previously state the DWI does, in majority of the cases, presents acute infarction and the FLAIR/DWI mismatch may help to identify potential salvage tissue. This method does not require perfusion imaging which may improve the generalizability of MR imaging in acute stroke management. The presence of large FLAIR hyper-intense region may signify proximal artery occlusion and may help to indicate the presence of irreversible tissue. Recently a large clinical study has been purposed to study the effect of thrombolysis in patients with wake-up-stroke using FLAIR/DWI mismatch as the surrogate marker of ischemic penumbra. Similar study is currently underway in Japan. A recent study with 41 patients presented
with unknown time of onset of stroke were assessed using the FLAIR/DWI mismatch. The investigator reported improved clinical outcome in patients who were selected based on FLAIR/DWI mismatch and achieved reperfusion via thrombectomy or thrombolysis and thrombectomy.\textsuperscript{320}

However, the identification of the FLAIR hyper-intense is based upon visual assessment and doubts have been raised regarding its reliability, sensitivity and specificity in predicting the stroke onset time. \textsuperscript{321, 322} Emeriau et al utilised 3 Tesla MR to study the FLAIR/DWI mismatch and concluded that it has a relatively low sensitivity and specificity in identifying mismatch at less than 4.5 hours of stroke onset. \textsuperscript{323} A recent study by Fahed et al reported the inter-rater FLAIR/DWI agreement was only moderate with $k= 0.43$ and only 61.1\% of raters reached a substantial intra-rater agreement.\textsuperscript{324} Again, this study showed the difficulty in the assessment of FLAIR images.

\textit{Despite these uncertainties, in the recently published WAKE UP study the FLAIR/DWI mismatch has been shown to reliably identify a cohort of patients with stroke of unknown time of onset who will response favourably to thrombolytic therapy.} \textsuperscript{325}

\textbf{2.4.4 Susceptible Weighted Imaging (SWI)/DWI Mismatch}

Susceptible weighted imaging is often used to identify cerebral hemorrhages but it can also show vessel anatomy and thrombus.\textsuperscript{326} Recent studies have shown that SWI can detect changes in cerebral tissue oxygen demand or consumption by multiple vessels with hypointense signals which may represent the DWI/PWI mismatch region and also the collateral status.\textsuperscript{327-329} Park et al studied a group of 10 patients with SWI/DWI mismatch and demonstrated good collateral flow suggesting the existence of such mismatch may correlated with good clinical outcome.\textsuperscript{330} The issue with SWI/DWI mismatch is that it is a qualitative measure since the mismatch boundary is defined by multiple blood vessel group. In addition,
the level of significant hypointensity is a subjective assessment. Future study in the thresholding of these hypointensity signal may be of benefit.

2.4.5 DWI/ASPECT Mismatch

A recent study looked at the interrater reliability of DWI/ASPECT mismatch and reported low correlation which makes DWI/ASPECT mismatch somewhat irrelevant in the era of advanced perfusion imaging. 324

2.4.6 Collateral Circulation Assessment

Large vessel occlusion (LVO) such as internal carotid artery or middle cerebral artery occlusion often result in large penumbral mismatch and without reperfusion the clinical outcome usually poor. The survival of the ischemic penumbra during the time of LVO is strongly influenced by the collateral circulation status. Logically the better the collateral circulation supply the longer the penumbra can sustain and better clinical outcome. Poor collateral circulation in patients LVO is correlated with poor clinical outcome, larger infarct core despite successful recanalization 331-334 even for posterior circulation stroke. 335 On the contrary the presence of good collateral circulation is associated with good clinical outcome 336-339 and good collateral status also correlates with good response to reperfusion therapy. 340-343 In a recently study by Boulouis et al 316 patients transferred from referral hospital to an endovascular expert center for thrombectomy. Collateral vessel status demonstrated the highest adjusted odds of 5.14 for poor clinical outcome. 344 Hence even when patients transfer from referral centre to major hub to receive thrombectomy if the collateral circulation status was poor then the clinical outcome of the patients remained poor despite reperfusion therapy. Indeed, the status of the collateral circulation is so important that its status is more important than the initial NCCT ASPECT score. 345 Using MRI FLAIR sequence good collateral flow could even delay the FLAIR signal changes (infarction) in patients with acute ischemic stroke. 346
The volume of the penumbra reduced with time in patients with poor collateral circulation while patients with good collateral circulation the penumbra volume remained the same in the first 6 hours of stroke onset. Indeed, this is the paradoxical phenomenon recently described by Alert et al.\(^347\) The traditional thinking for the penumbral concept is “Time is Brain”, however the data from DEFUSE 3 study showed the respond to ECR reperfusion therapy was time independent. This is a reflection of the selection of patients using perfusion imaging, hence patients with target mismatch. Patients with target mismatch at this late time window have relatively good collateral circulation which is sustaining the penumbra. To some extend this cohort of patients are self-selected being a good responder to ECR therapy. Tsai et al has elegantly explained this pheromone by showing that patients with target mismatch (good collateral circulation) their response to ECR and the potential of favourable outcome was independent of time while patients with malignant mismatch (poor collateral circulation) their chance of favourable outcome diminished rapidly with time.\(^348\)

2.4.7 Which mismatch to use?

The aim of the mismatch assessment is to identify the cohort of patients with acute ischemic stroke who will response to reperfusion therapy. Perfusion/Core mismatch has firmly established to be best tool for the selection of patients for ECR as demonstrated by EXTEND IA, SWIFT PRIME, EXTEND IA TNK and DEFUSE 3.\(^{287, 298, 349, 350}\) The result of DAWN also put clinical/Core mismatch as a validated alternative method. MRA/Core mismatch may be more applicable in centres where perfusion imaging is not available or for patients who have contraindication to contrast (such as allergy or severe renal impairment).\(^{314}\) FLAIR/DWI mismatch has been validated in the recent WAKE UP study.\(^{325}\) Collateral circulation can certainly assist in patient selection especially in the later time window. Currently there seems to be no clinical role at all for Clinical/CT ASPECT mismatch in the selection of patients for reperfusion therapy. The selection of the method is based upon the availability of the technology and expertise locally.
Suggested Changes: No page number

Response / Change: page numbers have been added

Previous page: 54
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Suggested change: 2.1.1. The relationship

Response: 2.1.1. The Relationship

Previous Page: 130
Current Page: 100

Suggested Change:

- Meaning of the following conclusion is not clear: “3.7 Conclusion
The following four chapters will detail the studies and their findings.”. Is this a conclusion or results?

Response:

3.7 Conclusion

This chapter has provided detailed description of the aim, hypotheses, patient recruitment criteria, imaging analysis method of the penumbral studies which form the bases of this thesis.

Examiner 2

Previous Page: 40
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Suggested changes:

Chapter 1 on ischaemic stroke was inclusive and gave a thorough and up-to-date overview of risk factors and their management as well as acute ischaemic stroke therapy. The last section on neuroprotection agents raises important questions as to their lack of success and it would have been useful for the candidate to have expanded on the underlying reasons for this failure.

Response / changes:

I have inserted additional information which is highlighted by bold and italic below.

1.5.5 Neuroprotection agents

Besides the need for reperfusion of the occluded vessels, neuroprotection has been investigated as a potential therapy for acute stroke management. This may prolong the survival of the cerebral tissue until reperfusion occurs. Unfortunately, in spite of very good evidence of efficacy of a variety of classes of compounds in animal models of ischemic stroke, translation of this into the human paradigm has proven to be extremely difficult. Indeed, a phase 3 study of the neuroprotective agent (NXY-089) failed to show clinical benefit when it was applied in patients with acute ischemic stroke, and more recently the ICTUS study failed to showed benefit of Citicoline in the management of moderate to severe acute ischemic stroke. The repetitive negative results of neuro-protective studies has resulted in a lull in further clinical trial activity.

The concept of neuroprotection in acute ischemic stroke has been around for a long time and more than a thousand experimental compounds have been tested but only a handful of these compounds demonstrated enough pre-clinical evidence of efficacy to have made it into randomised control clinical trial but, up till now, none have been proved to be effective.
in human. The lack of rigorous approach to the design and testing of these compounds has led to the establishment of the Stroke Therapy Academy Industry Round Table (STAIR) pathway but we are still far from identifying an effective neuroprotectant. In the era of highly effective ECR therapy one may think that the need of neuroprotection has diminished significantly. On the contrary there should be even more interest in the search for an effective neuroprotectants for two reasons. Firstly, despite ECR’s powerful treatment effect there are still a proportion of patients who still have unfavourable outcome despite ECR and not all stroke patients are eligible for ECR. Secondly the success of ECR has brought us unique insight into the pathophysiology of acute ischemic stroke with reperfusion.

To pave the way forward for the identification of an effective neuroprotectant one must try to understand the reasons for such failure in the translation of neuroprotection compounds from bench to patients. There are many reasons for this failure and majority is due to the differences between the animal and human model such as heterogeneous patient population, different age group, lack of co-morbidities in animal, mode of stroke induction, variable aetiology in patients, mainly MCA territory in animal, controlled environment in animal, and difference in outcome assessment.

NXY-059 was one of the most promising neuroprotection compound which was put through the rigorous STAIR pathway. Its phase 2 study showed promising neuroprotection properties (SAINT I) but when it was tested in a phase 3 study (SAINT II) it failed to show any neuro-protective effect. A recent study by Howell et al explored the reasons for its failure. This study tested NXY-059 in stem cell derived human neuron which clearly demonstrated the lack of any neuroprotective effect. Interesting a cocktail of neuroprotectant including ascorbate, reduced glutathione, and dithiothreitol used as a positive control showed neuroprotective effect. This study reflected that bias and assumption might have led to the failure of NXY-059.

The powerful treatment effect of ECR is due it rapid and effective reperfusion hence reperfusion is the key to neuronal survival. Reflecting on this concept, it might be
inappropriate to concentrate effort on just complete vessel occlusion animal model. Neuro-protection may be more effective if it is accompanied by effective reperfusion and act as a complementary therapy. Timing is also a crucial factor since “time is brain”. FAST-MAG tested magnesium in the pre-hospital setting to reduce the potential time delay in the administration of the neuroprotectant to the ischemic tissue. The failure of this study might be partly due to the heterogeneity of recruited patients which might have included patients with large infarct core and lack of reperfusion. NaI/Tat-NR2B9c inhibits the interactions of the synaptic scaffolding protein PSD95 with N-methyl-D-Aspartate glutamate receptors which augment the pro-death cellular pathway. ESCAPE NA-1 is a promising study which combines these important factors. It employs advanced neuroimaging (small infarct core and good collateral circulation) to recruit patients which will reduce the heterogeneity suffered by FAST MAG. The rapid reperfusion by ECR may help to enhance the effect of neuroprotectant.

Majority of the tested neuroprotectants acted on a single target of the ischemic cascade. The interaction of the inflammatory and immune system is complex and changes with time (such as microglial cells changed from protective phenotype (M1) to inflammatory phenotype (M2) over time). Hence interfering a single target within a complex system may be ineffective. It may be worthwhile to consider immunomodulation rather than just neuroprotection and, more importantly, to target multiple pathways of the immune or inflammatory system. Immunomodulation is not simply immunosuppression or anti-inflammation but also augment the immune response to ischemia. However, it may be difficult to design an agent which can act in such wide range of actions. Targeting immunomodulation also extends the potential therapeutic time window since the innate and adaptive immune response takes place over days not hours. The adaptive immunosuppression usually takes place after 48 hours. Natalizumab, a humanised monoclonal antibody against glycoprotein alpha-4-integrin which are expressed on the surface of the lymphocytes and monocytes. Despite its success in animal model, like all other neuro-protectants, failed to replicate such success in human model. This failure might be explained by the non-selective inhibition of lymphocytes and neutrophils.
Human amniotic epithelial stem cells (heSC) are harvested from human placental tissue with immunomodulation effect. In both mice and marmoset model, the administration of heSC within 24 hours or even up to 3 days after temporary or permanent occlusion model there was an effect on freezing the infarct core expansion and improve functional outcome. More importantly heSC can be administrated via intravenous injection in the acute phase of stroke compare to other neuro-regenerative stem cell therapy which requires culture and re-plantation of the stem cell into human tissue. Similar to ESCAPE-NA1 heSC has the potential to be given acutely to patients who receive ECR based on the presence of target mismatch to achieve the best outcome. I-ACT (ACTRN 1261800076279p) is a phase one clinical trial studying the safety profile of heSC in acute stroke patients within 24 hours of onset. However, this group of patients will not receive any reperfusion therapy since this may affect the study of the safety profile of heSC.

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Suggestion:

The introduction to collateral circulation as an important emerging area of imaging which may have major clinical correlations is highly relevant and it would have been of interest to expand this section.

Response:

2.4.6 Collateral Circulation Assessment

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Finally, the discussion of inflammatory pathways underlying the ischaemic event is an excellent return to basic science. The candidate might consider using molecular targets as
another approach to penumbral imaging at a molecular level which is a future direction of exciting possibilities.

Responses:

**Molecular Penumbra Imaging**

Despite the identification of inflammatory cascade and numerous potential markers for molecular imaging of the ischemic penumbra, molecular imaging are not yet applicable in clinical practice due to difficulty in accessing ligands in acute stroke setting, complexity if imaging requirement, delay in tracer imaging and lack of clinical validation.

PET imaging of ligands representing inflammation has been studied over the last decade. $^{11}$C-PK11195 binds to the translocation protein 18kDa/peripheral benzodiazepine receptor which reflects the activation of microglial and macrophages within the ischemic core. However, the uptake of $^{11}$C-PK 11195 extended peripherally and even to distant locations such as the thalamus representing future Wallerian degeneration.$^{414-416}$ Recently Abid et al reported the feasibility of MRI and PET PK 11195 imaging in patients with acute intracranial haemorrhages.$^{417}$ However, the clinical application of $^{11}$C-PK 11195 is still unclear.

**Imaging of the blood brain barrier (BBB) break down is potential way to study the region of ischemic brain. MRI has been the main imaging modality for the BBB study. There are two ways to study BBB break down using MRI, one method is static T1-weighted images and the other way is a dynamic contrast enhanced MRI. They were initially used to predict the risk of cerebral haemorrhages after stroke but the result was disappointing. More importantly MRI access is often limited in acute stroke setting and this makes post-contrast CT a more feasibly modality.$^{418}$**
One of the potential benefit of molecular imaging in ischemic stroke is to assess the potential efficacy of anti-inflammatory compound in stroke management. Recently Gauberti et al used ultra-sensitive molecular MRI to study the expression and activity of VCAM-1 in vessel occlusion and haemorrhage model in mice. The activities and expression of VCAM-1 should reflect the inflammation activities and the team also studies the effect of celecoxib and atorvastatin on VCAM-1 activities. The region of increased VCAM-1 activity might be seen as the inflammatory penumbra surrounding the ischemic core.419

Future development of imaging the inflammation penumbra may assist the development of neuroprotectants and immunomodulant.
Response: Changes made on page 60

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Suggested changes: 1st paragraph, 3rd line – correct spelling "alteplase"

Response: Changes made on page 74

Previous Page: 79

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Suggested changes: – 2nd paragraph, 4th line – correct “3 to 4 slices compared to 12 to 19”

Response: Changes made on page 71

Previous Page: 84

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Suggested changes: 1st paragraph, 2nd sentence – correct “Time of flight”

Response: Change made on page 78

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Suggested changes: 1st paragraph, 3rd sentence – insert “is it does”

Response: change made on page 78
The ischemic penumbra - its topography, duration and clinical effect

Date:
2018

Persistent Link:
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File Description:
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