post hoc quantitative assessment across all three CT perfusion profiles, illustrating the well-known intrinsic limitations of visual assessment based on vendor displays. Ultra-fast and reliable quantitative processing software that can be incorporated into daily practice is therefore needed if the findings from this study are ever to be tested formally in prospective studies or applied in routine practice.

Another caveat is the lack of consensus in the literature about optimum thresholds and processing methods to identify the penumbra and core using CT perfusion. Although the imaging definitions applied in this study have a sound basis from previous work, this is another area that needs clarification. Additionally, not all patients underwent CT angiography, so vessel occlusion site data are incomplete. A further point relates to lacunar strokes ($n = 37$), a group belonging to the non-mismatch profile that did not respond to thrombolysis, and for which no subgroup analysis is presented. Post hoc analyses of the early thrombolysis trials claimed that patients with lacunar infarcts benefitted just as much as others. It therefore remains unclear what the optimal treatment strategy for this group would be.

In summary, the study by Bivard et al. makes a strong case for CT perfusion-based selection for thrombolysis in an early time window. Although only a randomized comparison would establish the conclusions of this work beyond reasonable doubt, the study findings are convincing. Emerging randomized trial evidence with CT perfusion-based phenotyping for intravascular interventions (Campbell et al., 2015) and newer thrombolytic agents (Parsons et al., 2012) showing unprecedented rates of good outcomes further support the case. Perhaps heterogeneity of findings in early trials will be clarified in due course by physiological imaging-based studies. The use of CT perfusion to select the responders to intravenous therapy beyond 4.5 h is another area in need of prospective studies.

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doi:10.1093/brain/awv120

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Progranulin protects against the tissue damage of acute ischaemic stroke

This scientific commentary refers to ‘Multiple therapeutic effects of progranulin on experimental acute ischaemic stroke’, by Kanazawa et al. (doi:10.1093/brain/awv079).

Stroke is one of the commonest causes of death, and survivors often suffer debilitating impairments of speech, memory, movement, swallowing and other neurological functions. About 80% of strokes are ischaemic, due to thrombosis or embolism. The resultant loss of oxygen to the affected tissue depletes cells of energy and initiates a series of biological events that
include the release of toxic levels of glutamate, the production of free radicals, inflammation, and blood vessel disruption. The infarct, or the region of cell death at the ischaemic core, is surrounded by an area of damaged but still living brain tissue known as the penumbra. The injured but living cells of the penumbra can be restored to functionality if the infarct is prevented from expanding into this region by, for example, restoring blood flow through early administration of the thrombolytic protein tissue plasminogen activator (tPA). Very few other drugs have proven beneficial in limiting stroke-related damage in the human brain (Donnan et al., 2008). The penumbra has been described as a transition zone where processes of cell death and injury radiate outwards from the infarct to confront counteracting mechanisms of repair that are mobilized by the brain to protect the damaged tissue (Lo, 2008). In this issue of Brain, Kanazawa and colleagues provide important insights into how a secreted protein, progranulin, protects the brain from further damage after an ischaemic stroke and suggest that progranulin-dependent FTD (Kanazawa et al., 2015).

Progranulin has both neurotrophic and immunomodulatory actions (Toh et al., 2011). It is not specifically a brain protein, being widely distributed in epithelial and haematopoietic cells, but it is critically important in the brain. Mutational inactivation of a single allele of the human progranulin gene (PGRN) causes frontotemporal dementia (FTD), a cortical neurodegenerative disease. Progranulin-related FTD shows a distinctive histopathology in which affected neurons accumulate intracellular inclusions of a modified and ubiquitinated form of a protein called transcriptional response element DNA-binding protein (TARDBP, also known as TDP-43) (Toh et al., 2011). It has previously been shown that cerebral ischaemia prompts neurons to translocate TARDBP from the nucleus to the cytosol, where it is modified, recapitulating the initial stages in the development of the overt TARDBP proteinopathy of progranulin-dependent FTD (Kanazawa et al., 2011). If TARDBP is implicated in the neuronal response to stroke, does it follow that progranulin is involved too?

Kanazawa and colleagues found that progranulin levels are dynamically regulated in the ischaemic brain. Within 24 h of transient occlusion of the middle cerebral artery, progranulin levels increased in penumbral endothelial cells, microglia of the ischaemic core and in neurons of the penumbra, whereas in the dead and dying neurons of the central infarct PGRN expression was lost. By studying the glycosylation patterns of progranulin, Kanazawa et al. ingeniously showed that progranulin in the infarct is most likely produced by microglia, while that in the penumbra is produced by neurons. Clearly, progranulin expression responds to an ischaemic challenge, but does this mean there is a functional role for progranulin in the response to ischaemia and reperfusion? To answer this, the authors turned to progranulin knockout mice (PGRN KO). The outcome of ischaemia/reperfusion was significantly worse in the brains of PGRN knockout mice than in their wild-type counterparts. Infarct size was unaffected but oedema volume in PGRN knockout mice was considerably greater after 24 h and neurological defects were exacerbated. By 72 h, however, both wild-type and PGRN knockout mice were equally severely impacted in all tests suggesting that the endogenous progranulin levels of the wild-type mice had slowed but not eliminated the progression of the injury. In cell culture, progranulin had a small but significant cytoprotective effect by reducing neuronal death caused by oxygen and glucose deprivation, and prevented mobilization of TARDBP. To further test the hypothesis that progranulin is protective against stroke, Kanazawa and colleagues tested the ability of recombinant progranulin to attenuate the

Figure 1 Progranulin knockout and progranulin intravenous injection have mirror image effects on stroke severity (Kanazawa et al., 2015). N/C = no change; N/R = not reported.
damage caused by cerebral ischaemia in rats. Middle cerebral artery occlusion was achieved using autologous thrombin. Reperfusion injury was initiated by injection of tPA after 4 h, at which time point tPA is no longer therapeutic but instead worsens the stroke damage. Immediately before tPA treatment the rats were injected intravenously with progranulin, or immunoglobulin as a control. Progranulin treatment reduced all the parameters of stroke injury that were tested, namely infarct size, oedema volume, haemorrhage, mortality and neurological impairment. Thus the loss of progranulin in the PGRN knockout mice sensitizes the brain to ischaemic stroke damage, while intravenous administration of progranulin reduces stroke damage in wild-type rats (Fig. 1).

Other groups have studied progranulin and stroke. Mice that express a progranulin transgene under the control of a non-specific promoter have smaller infarct areas and improved motor skills after middle cerebral artery occlusion than wild-type controls (Tao et al., 2012). Others found that intracerebroventricular delivery of progranulin 2 h after ischaemia reduced infarct size, oedema, and mortality and improved neurological functions (Egashira et al., 2013). Intracerebroventricular progranulin treatment reduced the infiltration of neutrophils into the damaged brain after reperfusion, suggesting an anti-inflammatory mechanism of damage control. In contrast, Kanazawa et al. found no difference in neutrophil or microglial numbers between the injured brains of PGRN knockout and wild-type mice. This was surprising since PGRN knockout mice typically display a markedly overactive cellular response to inflammatory stimuli (Toh et al., 2011). Kanazawa et al. did however detect a decrease in levels of the anti-inflammatory cytokine IL10 in the microglia of PGRN knockout mice, which supports the presence of an inflammatory phenotype for the PGRN knockout mice at the molecular level. Jackman et al. (2013) observed increased haemorrhage, a very pronounced leakage of the blood–brain barrier, a larger infarct size and impaired motor function in post-ischaemic brains of PGRN knockout mice. These results are consistent with those reported by Kanazawa and colleagues; however, the mechanism the two groups propose for the oedema is different. Jackman and colleagues focused on ultrastructural abnormalities in the blood–brain barrier of PGRN knockout mice and their increased sensitivity to the vascular permeability-inducing effects of platelet derived growth factor-CC. Kanazawa and colleagues found that vascular endothelial growth factor (VEGF), a protein that stimulates vascular permeability, is increased in the penumbral astroglia and endothelial cells. The increase in VEGF was greater in PGRN-knockout brains than wild-type but only at later stages, 72 h post-ischaemia, whereas the greater oedema of the PGRN-knockout mice is evident by 24 h. Microglia must be present to obtain an increase in VEGF from the astroglia, suggesting that the increased production of VEGF is a downstream response to the altered inflammatory dynamics of the PGRN knockout mice, rather than a direct consequence of the loss of progranulin.

The mechanistic differences between the studies do not detract from the main point; progranulin reduces the tissue injury that is caused by cerebral ischaemia/reperfusion. Kanazawa et al. emphasize a critical feature of progranulin action, namely its potential to influence multiple facets of damage control in the ischaemic brain. Thus progranulin ‘hits’ several potential therapeutic targets, acting on the vasculature, the inflammatory system through the suppression of neutrophil recruitment, and the ischaemic blood–brain barrier disruption. Kanazawa et al. have made an essential contribution to an emerging literature that consistently establishes the protective actions of PGRN in multiple brain pathologies. These include not only acute trauma such as stroke but also chronic diseases such as Parkinson’s (Van Kampen et al., 2014) or Alzheimer’s disease (Minami et al., 2014). Progranulin may, therefore, prove protective across a broad cross-section of brain diseases. Although it does not always follow that what works well in rodents is equally effective in humans, the results presented by Kanazawa et al. should, at the very least, accelerate further research towards the development of innovative progranulin-based treatments designed to reduce both the loss of life caused by strokes and the devastating neurological impairments that commonly afflict stroke survivors.

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doi:10.1093/brain/awv123

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Oculomotor abnormalities in posterior cortical atrophy: are they different from those in Alzheimer’s disease after all?

This scientific commentary refers to ‘Abnormalities of fixation, saccade and pursuit in posterior cortical atrophy’, by Shakespeare et al. (doi:10.1093/brain/awv103).

Posterior cortical atrophy (PCA) is a progressive degenerative condition characterized by a gradual loss of visual skills and other posterior cortical functions due to atrophy of parietal, occipital and occipito-temporal brain regions (Lehmann et al., 2011). It is associated with a relative preservation of memory, language skills and judgement until late in the clinical course. Core features of PCA include partial or complete Bálint’s syndrome (simultanagnosia, optic ataxia and ocular apraxia) and Gerstmann’s syndrome (acalculia, agraphia, finger agnosia), along with various combinations of visuo-spatial and visuo-perceptual impairments (Crutch et al., 2012), apparent despite an otherwise normal ophthalmological examination. In this issue of Brain, Shakespeare et al. (2015) compare and contrast eye movement abnormalities revealed by basic oculomotor tests in patients with PCA, typical Alzheimer’s disease and healthy controls, in order to determine the extent to which abnormalities in basic (lower-order) oculomotor function contribute to visuo-perceptual disturbances in PCA (Shakespeare et al., 2015).

Patients with PCA typically present when they are between 50 and 65 years of age (Crutch et al., 2012). One of the most important manifestations of PCA is simultanagnosia, an inability to synthesize the overall meaning of a visual scene despite being able to identify its individual elements; this should be suspected when a patient presents with an inability to read pseudo-isochromatic plates, despite intact colour vision (Beh et al., 2015). The relative rarity of PCA makes it difficult to recruit large cohorts, but recently the number of studies of this disorder, often referred to as the cardinal visual dementia and the most common atypical Alzheimer’s disease phenotype, has been increasing.

The study of eye movements in neurodegenerative diseases has also become increasingly common in recent years. Such studies aim to provide biomarkers for early disease, in some cases preclinical, to assist in the differential diagnosis of phenotypically similar syndromes and to monitor the effects of therapy. Many studies have concentrated on saccades, which are relatively simple to record and analyse, and can be tested with increasingly complex paradigms used to evaluate cognitive abilities. A number of different abnormalities have been found in Alzheimer’s disease, including hypometric saccades, prolonged saccade latencies, reduced peak velocities and disorganized visual scanning (Mosimann et al., 2005). However, the results of studies looking at the saccadic velocity and gain (saccade amplitude divided by target amplitude) in Alzheimer’s disease are mixed: some have detected impairments (Shafiq-Antonacci et al., 2003) whereas others have not (Garbutt et al., 2008). Despite these discrepancies, two consistent impairments of saccades have emerged from Alzheimer’s disease oculomotor research; first, a high frequency of saccadic intrusions during attempted fixation usually in the form of square wave jerks, confirmed in the study by Shakespeare et al., and second, visual capture by the target in the anti-saccade paradigm (Garbutt et al., 2008), in which the subject has to suppress a reflexive saccade to a peripheral target and execute an endogenously driven saccade to an equal and opposite location.

Smooth pursuit eye movements are also usually abnormal in Alzheimer’s disease, with an increased frequency of saccades during pursuit resulting from a reduced gain (eye velocity divided by target velocity) in the pursuit system (Fletcher and Sharpe, 1988). However, in addition, large-amplitude saccadic intrusions in the direction of target motion are also observed, probably reflecting increased saccadic distractibility.

Shakespeare and colleagues have used a battery of simple oculomotor paradigms to examine fixation stability, saccade generation and smooth pursuit eye movements. The ability of patients to disengage attention and generate targets for subsequent