benefit from guidance provided by advanced MRI methods.

Whether diffusion-derived alterations in the attentional networks observed by Besson *et al.* (2017) relate to electrophysiological anomalies, the underlying structural brain pathology, or cognitive metrics, remains unclear. Notably, data in healthy controls have provided evidence for substantial overlap between structural and functional domains (Honey *et al.*, 2007). In focal epilepsy, although impairments in resting state functional coupling seem to parallel morphological disruptions, only very few multi-modal MRI studies have specifically addressed this issue (Voets *et al.*, 2012). In this context, polysynaptic functional coupling, the putative basis of connectivity in the absence of direct structural connections, may complicate the interpretation of findings.

The study by Besson and co-workers, which attempts to quantify the complex phenomena at the basis of the spatiotemporal organization of the epileptogenic zone, is admirable and forms a strong methodological framework. Future efforts in the field of 'epileptomics' should aim to validate these models with non-invasive, whole-brain electrophysiological techniques, such as magnetoencephalography, and to integrate them with advanced structural and functional MRI. A coherent multidisciplinary approach will help determine whether connectome-based analysis of the epileptogenic network can be used to improve surgical procedures, including minimally invasive neuroablative methods, and to refine current MRI-based predictors of surgical outcome.

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Spreading depolarization and acute ischaemia in subarachnoid haemorrhage: the role of mass depolarization waves

This scientific commentary refers to 'Subarachnoid blood acutely induces spreading depolarizations and early cortical infarction', by Hartings *et al.* (doi:10.1093/brain/awx214).

Ischaemia is a common consequence of subarachnoid haemorrhage (SAH), affecting approximately 20–40% of patients (Jabbarli *et al.*, 2015). Some of these patients fall into the category of acute cerebral ischaemia (ACI), defined as signs of ischaemia on head imaging within 3 days of the bleed. ACI significantly increases rates of death and moderate-to-severe disability (Schmidt *et al.*, 2007), but its pathophysiology is incompletely understood. Intracranial circulatory arrest during aneurysm rupture and ultra-early vasospasm have been implicated, as has microvascular dysfunction, a process independent of large vessel pathology. An increasing body of literature suggests that subarachnoid blood may trigger cortical spreading depolarization and lead to early infarction (Bosche *et al.*, 2010). In this issue of *Brain*, Hartings and co-workers elegantly combine experimental with human data to examine whether subarachnoid blood is sufficient to induce spreading depolarization in the gyrencephalic brain, and provide evidence for spreading depolarizations as an underlying

element for ischaemia in SAH (Hartings *et al.*, 2017).

Spreading depolarization starts as a breakdown of transmembrane ion gradients, leading to massive ion translocation, neurotransmitter release, and cytotoxic oedema. In normal brain tissue, vasodilation increases regional cerebral blood flow to match the increased metabolic demand during membrane repolarization. In the injured brain, this neurovascular coupling is impaired. Erythrocyte breakdown products bind nitric oxide and impair vasodilation, while extracellular K^+ ions further constrict nearby vessels. Areas of spreading depolarization also show microcirculatory vasospasm, exacerbating the mismatch between energy supply and metabolic demand. Ischaemia results when a 'commitment point' is crossed—the threshold at which persistent depolarization causes permanent neuronal injury (Winkler *et al.*, 2012). In patients with SAH, erythrocyte breakdown products may trigger clusters of cortical spreading depolarization, leading to impaired neurovascular coupling and eventual ischaemia (Ayata and Lauritzen, 2015).

Using a swine model to best approximate a gyrencephalic brain during SAH (Muench *et al.*, 2007), Hartings *et al.* injected autologous blood onto the superior frontal and motor gyri. Normal saline or fibrin sealant were injected as controls for fresh or clotted autologous blood, respectively. Dural electrode strips and probes for brain temperature, intracranial pressure, brain tissue oxygenation ($P_{bt}O_2$) and regional cerebral blood flow were positioned for 6 h of monitoring prior to euthanasia. Brain slices were stained and digitally imaged to calculate infarct volumes. Findings revealed that subarachnoid blood was sufficient to provoke spreading depolarizations and spreading depolarization clusters. Cortical infarcts were strongly associated with clusters and thicker clots. Brain slices were also stained for cyclooxygenase-2 (COX-2), an enzyme involved in the conversion of arachidonic acid to prostaglandin H2, and implicated in platelet binding to endothelial tissue. Significant COX-2 upregulation was seen in comparison to the contralateral cortex, suggesting that spreading depolarizations may affect cellular function even in remote tissue.

Hartings *et al.* then expanded their study to assess the role of spreading depolarizations in human patients with aneurysmal SAH and early brain lesions. Patients with anterior communicating artery aneurysms, electrocorticography subdural electrode strip monitoring, and early MRI assessment (24–48 h after aneurysm treatment) were selected. Those with early ischaemic lesions near interhemispheric SAH had a markedly increased incidence of spreading depolarizations in the first 3 days after aneurysm rupture, in comparison to those without lesions. The patients with infarcts were noted to have significantly higher World Federation of Neurosurgical Societies (WNFS) SAH scores, and their extended Glasgow Outcome Scores were significantly lower than in patients without focal brain lesions.

From studies in both animals and patients, Hartings *et al.* have thus identified spreading depolarizations as an early, prominent component of the cortical response to subarachnoid blood, with a possible unique role in early infarct development. Spreading depolarization marks the onset of impaired cell homeostasis leading to massive ion translocation and cytotoxic oedema, and potentially to cell death (Dreier, 2011; Hartings *et al.*, 2017). The next steps are to assess whether spreading depolarization is a cause versus effect of early ischaemia, and to determine the appropriate means and timing for intervention. Though spreading depolarization has been studied in both extremes of ischaemic and normal tissue, the majority of spreading depolarizations likely have intermediate characteristics dependent on local tissue oxygenation, metabolic activity, and regional blood flow (Dreier, 2011). Spreading depolarization may follow as a consequence of impaired blood flow in SAH, or may arise directly as a result of neurotransmitter and vasoconstrictor release from subarachnoid blood products. Ketamine has been found to inhibit spreading depolarization in small clinical studies, and merits further investigation (Sakowitz *et al.*, 2009).

Lesion development depends on a given duration and order of spreading depolarization, metabolic crisis, and impaired neurovascular coupling (Ayata and Lauritzen, 2015). Anoxia or aglycaemia are the extremes of spreading depolarization. Spreading depolarizations provoked by chemical or ischaemic insults are likely not exclusive but synergistic, and may vary over time. Cell death may provoke ion shifts and neurotransmitter release, and sustained spreading depolarizations may impair neurovascular coupling and lead to tissue ischaemia. Further research is required to identify chemical or electrophysiological markers of the dominant process, and the threshold for the commitment point of ischaemia, in order to better time and target therapeutic interventions.

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