and this additionally contributes to locking patients into persistent pain states. Future work motivated by this fascinating study is required.

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Is the blood–brain barrier differentially affected by different variants of migraine?

This scientific commentary refers to ‘ictal lack of binding to brain parenchyma suggests integrity of the blood–brain barrier for $^{11}$C-dihydroergotamine during glyceryl trinitrate-induced migraine’, by Schankin et al. (doi:10.1093/brain/aww096).

In this issue of Brain, Schankin and co-workers study the permeability of the blood–brain barrier in six migraineurs and six control subjects at rest and during acute glyceryl trinitrate-induced migraine attacks without aura, using PET with the novel radioligand $^{11}$C-dihydroergotamine ($^{11}$C-DHE) (Schankin et al., 2016). This radioligand is chemically identical to pharmacologically active DHE, a potent drug for the treatment of migraine headache. While $^{11}$C-DHE was seen to bind to structures that lack a blood–brain barrier such as the choroid plexus and pituitary gland, no binding was observed in the brain parenchyma either at rest or during attacks. Specifically, no binding occurred in the hippocampus, which shows the highest density of the highest affinity DHE receptors, and the raphe nuclei, a postulated brainstem site of action during migraine. The study thus suggests that the blood–brain barrier remains closed during attacks of migraine headache. This may guide the future development of anti-migraine drugs because it indicates that targets outside of the brain parenchyma are involved to such an extent in the generation and maintenance of migraine headache that pharmacological modulation of these targets alone may antagonize the headache. In other words, it does not seem essential for anti-migraine drugs to directly interfere with central pain centres. The advantages are obvious in that CNS side effects could potentially be avoided.

Moreover, the study by Schankin et al. raises an interesting pathophysiological question. Migraine aura is assumed to be one of the clinical correlates of spreading depolarization. The term spreading depolarization describes waves of abrupt, sustained breakdown of neuronal transmembrane ion gradients and depolarization en masse in the brain. The same phenomenon also occurs in conditions other than migraine such as stroke and traumatic brain injury (Dreier and Reiffurth, 2015). In normally functioning tissue, spreading depolarization induces spreading depression of spontaneous activity because the sustained depolarization exceeds the inactivation threshold for action potential-generating channels. It is assumed that the patient perceives such spreading depression of activity as migraine aura if the spreading depolarization runs through perceptual and eloquent brain regions. In migraineurs, spreading depolarization may then trigger headache, which typically follows the aura.

While the present study found no evidence for opening of the blood–brain barrier in migraine without aura,
The effect of three pinprick-induced spreading depolarization and coworkers (2004) investigated in vitro to spreading depolarization nitric oxide enhanced susceptibility nitric oxide (NO), and yet reduced glyceryl trinitrate is converted to opening of the blood–brain barrier. In a rodent model, Gursoy-Ozdemir to regular migraine attacks with aura because spreading depolarization can cause opening of the blood–brain barrier under certain conditions, consistent with the abovementioned case studies in patients with familial hemipлегic migraine (Dreier et al., 2005; Cha et al., 2007). However, universal validity of this link cannot be derived from these findings.

In conclusion, future studies should address the question of whether blood–brain barrier opening is observed during or after unprovoked attacks of migraine aura. Such studies will face well known logistical challenges and, in the event that no opening of the blood–brain barrier is detected, will need to overcome the publication bias against negative results in a similar fashion to the study by Schankin et al. Unfortunately, in contrast to glyceryl trinitrate-triggered migraine headache, there seems to be no suitable trigger for migraine aura. In previous cerebral blood flow studies using 133Xe, the procedure of catheterizing and injecting the carotid artery provoked aura in more than 50% of migraineurs (Lassen and Friberg, 1991). However, such procedures carry a small risk of stroke and therefore cannot be recommended.

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Glossary

Cortical spreading depolarization: Waves of abrupt, sustained breakdown of neuronal transmembrane ion gradients and depolarization en masse in the brain, which propagate through the tissue at a rate of ~2–9 mm/min.

Cortical spreading depression: Spreading depolarization-induced cessation of spontaneous activity.
Bayesian inference, dysconnectivity and neuromodulation in schizophrenia

This scientific commentary refers to ‘Estimating changing contexts in schizophrenia’, by Kaplan et al. (doi:10.1093/brain/aww095).

The paper by Kaplan et al. in this issue of Brain addresses one of the most interesting questions in contemporary schizophrenia research: the role of uncertainty during perception (Kaplan et al., 2016). Uncertainty enjoys much interest in schizophrenia research as it may provide a crucial link between core clinical symptoms of schizophrenia—aberrant perceptual inference (e.g. hallucinations) and abnormal beliefs (delusions)—and longstanding neurobiological findings that patients with schizophrenia display widespread alterations in structural and functional brain connectivity (dysconnectivity).

These two cardinal features of schizophrenia have been integrated in disease theories, which have developed in three waves. A first influential proposal was that dysconnectivity in schizophrenia arises from abnormal regulation of NMDA receptor (NMDAR)-dependent transmission by neuromodulatory (dopaminergic and cholinergic) influences (Friston, 1998). Given the critical role of NMDARs for synaptic plasticity and myelination, this suggested that both neurodevelopmental aspects of schizophrenia (cf. abnormal pruning of connections by altered experience-dependent plasticity) and structural dysconnectivity might arise from a primary disturbance of NMDAR-dependent plasticity due to aberrant neuromodulatory control. Second, these putatively abnormal NMDAR-neuromodulator interactions (NNI) were proposed to cause a central computational impairment in schizophrenia: abnormal hierarchical Bayesian inference in the cortex (Stephan et al., 2006). This proposal was inspired by the notion that the brain constructs a hierarchical and probabilistic model of the world in order to infer the environmental causes of its sensory inputs (predictive coding), and by the increasingly discernible importance of NMDAR-neuromodulator interactions for implementing hierarchical Bayesian inference in the brain (Fig. 1). Under generic conditions, belief updates in Bayesian inference are driven by prediction errors (the difference between actual and predicted inputs) but, critically, weighted by how uncertain or precise both predictions and sensory inputs are. While prediction (error) signalling relies on glutamatergic transmission (NMDA and AMPA receptors), uncertainty-weighting may draw on tonic neuromodulatory signals, e.g. dopaminergic or cholinergic volume transmission. This view puts uncertainty (or its inverse, precision) at the centre stage in theories of schizophrenia. In a third step, this computational view of schizophrenia with its focus on uncertainty or precision has enabled the construction of bridges from neurophysiology to clinical symptoms and led to influential conceptualizations of perceptual aberrations and delusion formation in schizophrenia (Fletcher and Frith, 2009; Corlett et al., 2010; Adams et al., 2013).

While these theories are appealing in that they integrate physiological and computational mechanisms and link them to clinical symptoms, testing their predictions has been a slow process. This is partially because the necessary tools have been under development. Recent years, however, have seen major methodological advances in computational neuroimaging. For example, trajectories of individual belief updates, and how they are driven by prediction errors and uncertainty, can be inferred from individual behaviour by hierarchical Bayesian models (Nassar et al., 2010; Iglesias et al., 2013). Furthermore, dynamic causal modelling has made it possible to characterize effective (directed) connectivity between neuronal populations based on functional MRI or electrophysiological data.

The article by Kaplan et al. provides a compelling demonstration of how these techniques can be combined to probe hypothesized abnormalities of Bayesian inference and neuromodulation in schizophrenia. Using both hierarchical Bayesian