

accounting for maintained postoperative Stroop accuracy even in patients who did not benefit from intraoperative monitoring.

Innovative approaches such as that implemented by Puglisi *et al.* are likely to continue to expand the range of cognitive domains that can be monitored (and thus preserved) during surgery. These advances in surgical practice raise a wider dilemma: how to balance oncological benefit against treatment risks in the battle against incurable brain cancer. Maximal preservation of eloquent fibre tracts in the context of good tumour control should, intuitively, help to sustain long-term cognitive and neurological performance. However, even expert awake mapping does not prevent cognitive declines. Most often, such deficits are transient, reflecting the adaptive potential of the injured brain (Duffau, 2015). Indeed, remarkable levels of recovery in stroke and traumatic brain injury patients indicate that even white matter damage can to some extent be compensated for.

Currently, the extent to which higher-order cognitive deficits following right hemisphere surgery might be amenable to rehabilitation remains poorly understood. In contrast, the benefits to be gained from maximal resection are increasingly recognized. As all axonal connections contribute to function in some way, mounting evidence that the right hemisphere contributes in non-redundant ways to cognition highlights an important need for multidisciplinary approaches to

unambiguously tie intraoperative observations to long-term cognitive outcomes. Focused studies examining how much damage individual fibre tracts are able to tolerate, and what skills critically impact on quality of life, seem crucial to guide surgical strategies in the right hemisphere. Such an understanding will likely only arise from routine integration of longitudinal cognitive evaluations in the surgical pathway to link behavioural changes with specific structural damage. Such research seems especially urgent to improve treatment for patients with high grade glioma, who stand to gain (in quality of life) but also lose (in progression-free survival) substantially in the search for the optimal oncological-functional treatment balance.

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## Competing interests

The authors report no competing interests.

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# Bayesian inference and hallucinations in schizophrenia

This scientific commentary refers to 'Acquisition of visual priors and induced hallucinations in chronic schizophrenia', by Valton *et al.* (doi:10.1093/brain/awz171).

The principles by which sensations lead to percepts have puzzled scholars since ancient times (e.g. Plato's *Allegory of the Cave*). Around 150 years ago, von Helmholtz (1867)

proposed that perception corresponded to 'unconscious inference' about the causes of sensations. More recently, this Helmholtzian concept of perception has been formalized

mathematically under the framework of the ‘Bayesian brain’ (Friston, 2005a). Simply speaking, this assumes that the brain constructs a model of the world in which prior ‘beliefs’ (i.e. probability distributions) guide probabilistic inference about the causes of the noisy and ambiguous sensory inputs the brain receives. This general idea, which has become highly influential in research on perception as well as psychopathology, provides the foundation for the innovative behavioural study on schizophrenia by Valton and co-workers in this issue of *Brain* (Valton *et al.*, 2019).

While different concrete Bayesian models of perception exist, they refer to the same basic principle of perception: the integration of an initial prediction or ‘prior’ with new sensory inputs (‘likelihood’), resulting in a percept (‘posterior’), which represents an integration of the two sources of information that is weighted by their relative precision (inverse uncertainty). In other words, the higher the precision of one’s prior belief relative to the precision of the sensory inputs, the more strongly the percept (posterior) will be dominated by the prior. This implies that biological abnormalities in the way the precisions of prior beliefs or sensory data are represented neurally would lead to aberrant perceptual inference—a notion that now plays a central role in theories of mental disorders like schizophrenia (Friston *et al.*, 2016).

Psychotic symptoms in particular are now commonly examined from the Bayesian brain perspective and conceptualized as abnormal inference (Fletcher and Frith, 2009). This is often done in the context of hierarchical models, such as predictive coding (Rao and Ballard 1999; Sterzer *et al.*, 2018), where beliefs at different levels of an inference hierarchy serve as top-down predictions for lower levels and are themselves updated by ascending precision-weighted prediction errors. Historically, the first concepts of schizophrenia as a disorder of hierarchical Bayesian inference, due to abnormal predictive coding, were

proposed nearly 15 years ago (Friston, 2005b; Stephan *et al.*, 2006). These papers highlighted hallucinations as a symptom that might be explained by overly precise prior beliefs about the causes of sensory inputs, caused by aberrant neuromodulatory (cholinergic) transmission. Under such hyper-precise priors, a well-formed percept could arise from pure noise in sensory channels, in the absence of any external sensory input. This notion has received support from a recent computational study of experimentally induced auditory hallucinations, finding stronger priors in individuals experiencing hallucinations compared to those who do not (Powers *et al.*, 2017). However, alternative explanations of auditory hallucinations exist that also derive from a Bayesian perspective (for discussion, see Sterzer *et al.*, 2018).

The notion of abnormalities in perceptual inference offers a powerful framework for conceptualizing psychotic symptoms. However, mathematically, alterations of sensory precision and prior belief precision in opposite directions could lead to similar abnormalities of inferences. Careful experimental studies are therefore needed to disambiguate such alternative mechanisms. This is the challenge that the study of Valton *et al.* takes on, focusing on visual hallucinations.

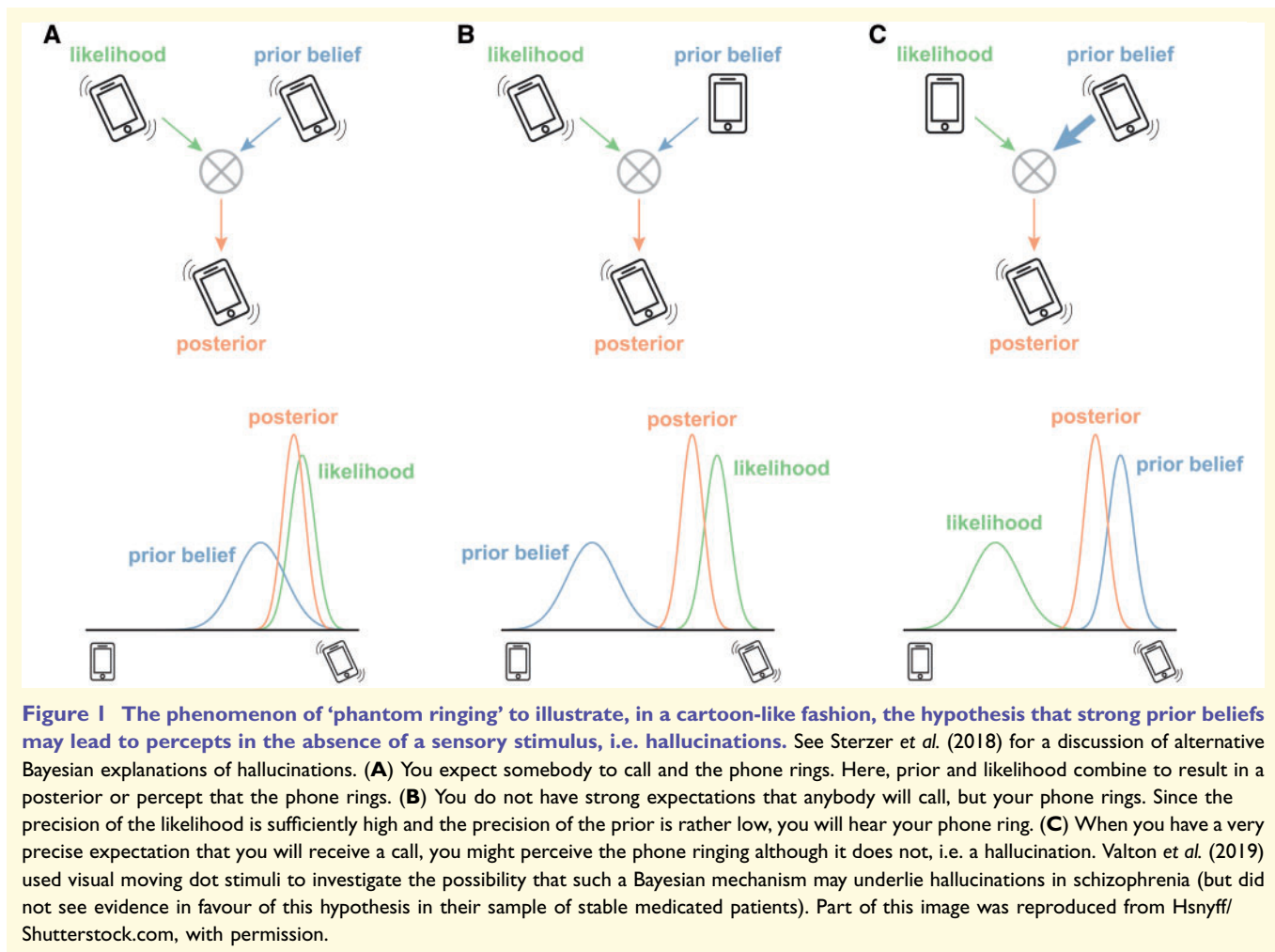
The authors assessed 20 individuals with schizophrenia in a stable, chronic and medicated state, as well as 23 healthy controls (with sample size guided by a power analysis assuming strong effect sizes). They used a previously established statistical learning task in which subjects are exposed to visual displays with coherently moving dots, with contrasts hovering around individual detection thresholds. In one condition, the participants had to estimate the direction of movement. Unknown to the participants some directions occurred more often than others. Analysing the bias towards these more frequently presented directions allowed for the assessment of implicit learning of stimulus statistics.

Additionally, the task included a detection condition, requiring judgments about whether any dots were present or not. Positive responses on trials when stimuli were absent or below detection threshold were counted as hallucinations.

Importantly, the authors also modelled subjects’ trial-wise responses using a variety of both Bayesian and non-Bayesian models and compared the models’ relative plausibility. In this way, they could determine whether an individual’s perception conformed to Bayesian inference at all and, if so, how priors were formed that shaped perceptual decisions. In particular, the authors were able to estimate both the precision of the acquired prior as well as the sensory precision.

Statistical model comparison showed that a Bayesian model of perception explained the data most plausibly in both groups. Patients and controls showed comparable acquisition of perceptual priors, which, in both groups, approximated the actual stimulus statistics. Neither the estimates of the precision of the prior nor of the precision of the sensory data were significantly different between groups. (Surprisingly, however, individuals with schizophrenia less often experienced a moving dot pattern when the stimulus was absent or when it was below detection threshold.) Overall, these results led the authors to question the theory of aberrant Bayesian inference in psychosis, at least for the visual domain and in chronic schizophrenia.

The study by Valton *et al.* is an important early step in the beginning investigation of schizophrenia as a disease potentially characterized by abnormalities of Bayesian inference. The behavioural paradigm is elegant, and the modelling approach is powerful in that it allows for disambiguating multiple potential abnormalities of perceptual inference. Nevertheless, there are also some important caveats—some of which are also discussed in the paper—that deserve consideration when integrating this



study’s conclusions with existing (e.g. Powers *et al.*, 2017) and future results.

First, it is generally challenging to construct experimental probes of perceptual inference that approach the phenomenology of symptoms experienced in psychosis. The visual paradigm used by Valton *et al.* is elegant but does not well match the type of visual hallucinations in schizophrenia that are phenomenologically considerably more complex (often involving fully formed percepts of people, animals, or faces; Waters *et al.*, 2014) than the simpler dot-motion stimuli in this paradigm. This is not a trivial issue as a difference in induced versus spontaneous hallucinatory contents would imply that the experimental induction of hallucinations affects a different neural circuit than the one involved

in the ‘natural’ symptom. It is also not clear whether a perceptual mechanism found in relation to visual hallucinations would necessarily hold equally for (the clinically far more frequent) auditory hallucinations in schizophrenia: existing Bayesian theories of psychotic symptoms do not state explicitly whether abnormal inference is expected to be specific for a particular circuit and/or sensory modality, or should generalize across circuits/modalities. This leaves open whether a null result obtained for a particular modality or circuit would be sufficient to refute existing Bayesian theories of psychotic symptoms in general.

Second, the reported lack of differences in Bayesian inference between patients and controls should be interpreted with caution. The sample consisted mostly of patients whose

positive symptoms ranged from none to mild, and patients did not report hallucinations significantly more often than controls. In addition, the clinical score of hallucinations used in this study (item P3 of the Positive and Negative Syndrome Scale, PANSS) does not differentiate between types of hallucinations (e.g. auditory versus visual), therefore the actual occurrence of visual hallucinations in this sample is not clear. Finally, while there were no significant group differences in the frequentist tests, the study was powered to detect large effect sizes, and with Bayes factors close to three the corresponding Bayesian tests did not provide strong evidence in favour of the null hypothesis.

Third, the diagnosis of ‘schizophrenia’ likely subsumes patients in which heterogeneous disease

## Glossary

**Bayesian inference:** The updating of prior beliefs in the light of new observations, based on the rules of probability theory, resulting in a posterior belief.

**Likelihood:** A function that indicates how likely some given observations (data) are under different values of an unknown parameter  $x$ .

**Prior:** A prior belief about an unobservable parameter  $x$  that is expressed as a probability distribution  $P(x)$ .

mechanisms lead to similar symptoms. Notably, the mathematical form of Bayesian belief updating implies that similar abnormalities of inferences could arise from opposite alterations of sensory precision and prior belief precision—which, in turn, might be caused by different abnormalities of neuromodulatory processes (Friston *et al.*, 2016). This heterogeneity is important to keep in mind when considering inconsistent results between investigations of perceptual inference in schizophrenia (*cf.* Powers *et al.*, 2017). More generally, it calls for prospective studies that examine whether differential impairments of Bayesian inference are linked to different biological alterations and distinct clinical trajectories.

Notwithstanding these caveats, the study by Valton *et al.* represents an important early step on the path towards clarifying the nature (or absence) of abnormal Bayesian inference in schizophrenia. It not only illustrates the power and elegance of computational approaches to understanding perception, but also serves as an important reminder of the complex relation between computational theories of psychopathology, experimental induction of symptoms, and the heterogeneity of syndromatically defined psychiatric disorders like schizophrenia.

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