Commentary on: Visual Hallucinations Are Characterized by Impaired Sensory Evidence Accumulation: Insights From Hierarchical Drift Diffusion Modeling in Parkinson's Disease by Claire O'Callaghan et al

Precision psychiatry

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It is a pleasure to comment upon O'Callaghan *et al's* work on hallucinations in Parkinson's disease (1). Not only was this a compelling piece of neuroscientific psychiatry, it also serves as a vehicle to briefly review developments in computational psychiatry over the last decade (2). O'Callaghan *et al* characterized sensory processing during perceptual decision making in Parkinson's disease patients with and without hallucinations. Using a normative (drift-diffusion) model (DDM) they quantified the rate at which participants accumulated sensory evidence. Their results indicate slower rates of evidence accumulation in patients with hallucinations; speaking to "inefficient and less flexible sensory evidence accumulation" as a unique feature of hallucinators. They then make an important move and relate the normative (descriptive) characterization of perceptual inference to hierarchical predictive coding formulations of perception that now predominate in the cognitive neurosciences (3). There are many reasons that this exemplary application of computational neuroscience to psychopathology could be applauded. I will focus on three.

First, it illustrates the potential of computational psychiatry – a movement that is gaining increasing traction as a way to formalize, quantify and phenotype neuropsychiatric syndromes. In particular, linking an established normative model (DDM) to a process theory – such as predictive coding – shows that psychophysics and computational phenotyping can be meaningfully interpreted in terms of both brain function and physiology. This provides a mechanistic entree into the pathophysiology that may underlie many psychiatric symptoms and signs. So why did the authors focus on evidence accumulation and predictive coding?

The second theme highlighted by O'Callaghan *et al* is, I think, fundamental. In the search for a functionalist framework – within which to understand phenomena such as hallucinations and delusions – one has to confront the question: "what sort of failures do these phenomena belie?" If the answer is "failures of decision making and perceptual inference", then we know immediately the right sort of theoretical framework must explain things like perceptual inference, belief-updating and evidence accumulation. This then leads to the key notion of *false inference* as the single most important psychopathology that underlies most psychiatric conditions – and many neurological syndromes. This is why the Bayesian brain and predictive coding have proved such a useful point of reference when trying to understand psychopathology. So how can inference go awry?

The third theme – that I want to pick up on – is the central role of encoding uncertainty or *precision*[1] in the brain. In what follows, I will try to explain the notion of precision and how it provides an explanation for psychopathology at a purely functional level while, at the same time, connecting to synaptic and molecular levels of explanation; ranging from synucleinopathies through to neurotransmitter theories of schizophrenia. The precision story in (computational) psychiatry emerged, over the past decade, hand-in-hand with the paradigm shift in cognitive neuroscience from sandwich models of brain function[2] to predictive coding and active inference.

For me, this story starts 12 years ago when writing another commentary on Collerton *et al's* treatment of complex visual hallucinations (4). How could one account for hallucinations and hallucinosis in organic psychosyndromes (e.g., Lewy body disease), in terms of aberrant perceptual inference? The answer on offer at that time was an improper evaluation of the relative uncertainty or precision of sensory evidence, in relation to prior beliefs about the causes of sensations. This may sound a bit abstract but is basically saying that you will make some very odd inferences if you cannot estimate the standard error necessary for statistical hypothesis testing. A failure to properly encode the precision – that should be afforded sensory evidence – would therefore lead to a pernicious form of false inference; with ample opportunity for false positives (e.g., hallucinations and delusions) and false negatives (e.g., agnosia and neglect). For those people who have not come across precision before, it is probably best understood in the context of predictive coding:

Predictive coding is a process theory (of how the brain might implement hierarchical inference) that appeals to long-standing notions of brain function that can be traced back to Kant, through Helmholtz's notion of unconscious inference through to Gregory's ideas about perception as hypothesis testing (5).

[1] Precision is a statistical quantity that is the complement of variance, dispersion or entropy. Because entropy is the mathematical measure of uncertainty, a high precision corresponds to low uncertainty.

[2] The sandwich model assumes three stages of information processing: perception, cognition and action that follow each other in a sequential fashion. This (classical) model has now been superseded by a more constructivist and enactivist view of brain function that entails recurrent neuronal processing – and a circular causality among processing stages (and the world).

In brief, predictive coding rests upon the formation of prediction errors. These are the differences between top-down or descending predictions of sensory input and the sensations we actually sample. The resulting prediction errors and then passed to higher levels of the cortical hierarchy to update neuronally encoded expectations or representations of how those sensations were caused. This recurrent form of belief-updating or propagation thereby entails the reciprocal exchange of ascending prediction errors and descending predictions that ultimately lead to hierarchical inference to the best explanation for the sensed (lived) world (6).

On this view, prediction errors can be regarded as newsworthy information that has yet to be explained – information that is assimilated or accumulated via a process of Bayesian belief updating. Crucially, there are many sorts of prediction errors – in many modalities – and the brain has to decide which predictions to attend to. This is where precision comes in. In a Bayesian brain, prediction errors that convey precise, reliable, high-quality information are afforded greater precision or weight, such that they have a greater influence on perception. Psychologically, this is nothing more than attending to the right sort of newsworthy information and attenuating imprecise or 'fake' news. Physiologically, this precision engineered selection – of the right sort of prediction errors – is thought to be mediated by the synaptic gain mechanisms associated with attentional gain (7). These come in a variety of flavors; ranging from classical neuromodulatory synaptic mechanisms, through to excitation-inhibition balance and related mechanisms based upon synchronous gain (i.e., the dynamical selection of prediction errors through fast synchronized population activity that is orchestrated by inhibitory interneurons). It is this mechanistic bridge between a fundamental computational imperative to properly balance sensory evidence against (hierarchical) prior expectations and plausible neurobiological mechanisms that links psychopathology and pathophysiology. This is particularly pertinent in conditions like Parkinson's disease, where not only do we have an abnormality of classical neuromodulatory (i.e. dopamine) neurotransmission but also selective loss of the neuronal infrastructure that maintains cortical excitability and the gain control required for dynamic sensory attention and attenuation. One can see how such a ubiquitous computational mechanism (i.e., the evaluation and deployment of precision) could be the target of pathophysiology – from failures of neuromodulation to neurodegeneration. Furthermore, the domain specificity of these failures has exactly the same latitude as functional specialization in the brain *per se*. This follows because every system – from the visual to the visceral –

will be equipped with its own precision control mechanisms.

The precision story has unfolded at an enormous pace. Shortly after its inception to explain hallucinations and delusions; e.g., (8), it fostered a research paradigm in autism that can be succinctly summarized as a failure to attenuate sensory precision (9). Exactly the same theme has now been applied to nearly every psychiatric syndrome and symptom (see Table 1). For example, it has been pursued in the context of schizophrenia, depression, hysteria, fatigue, stress, thought insertion *etc*. The common theme is a failure to balance sensory evidence against prior beliefs, due to aberrant precision control. This aberrant precision transcends the actual content of the beliefs (or evidence). In other words, it speaks to a second order failure to properly evaluate and respond to *uncertainty* in a capricious world. There are many intriguing lines of argument that one could pursue here; however, I will close with a strategic observation and direct interested readers to the (selected) papers in Table 1.

It is tempting to make much wordplay with 'precision' (10); for example, the precision engineering of neuronal circuits above. Another obvious wordplay would be in relation to precision psychiatry – in the sense of precision medicine (that rests upon individualized therapeutic regimes informed by high-dimensional biometric data). However, in the current setting, precision psychiatry could take a different meaning that calls on the computational and neurophysiological constructs above. I mention this because there may be an interesting connection between the two meanings. This rests upon a mathematical theorem called the *complete class theorem*. This says that, for any (Bayesian) decision or behavior and a given loss function, there exists prior beliefs that render the behavior Bayes optimal. At first glance, this may appear to subvert Bayesian formulations of false inference in psychiatry – because it means one can tell a 'just so' story about any abnormal behavior. However, a deeper analysis suggests that Bayesian formulations of psychopathology must, by the complete class theorem, exist. Furthermore, any behavior can be uniquely characterized in terms of prior beliefs. This means that every patient is uniquely characterized by her prior beliefs that can be quantified using the sorts of procedures described in O'Callaghan *et al*. If we equip this quantification with a plausible process theory, we have a formal framework in place to phenotype and understand false inference in psychiatry, even if it has yet to be specified precisely (*sic*).

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Table 1: a selection of recent papers dealing with predictive coding, hallucinations and psychiatry (selected from a PubMed search for predictive coding AND psychiatric syndromes).

Syndrome or symptom	***selected papers***
Precision, predictive coding and Bayesian inference in **schizophrenia**	*1: Randeniya R, Oestreich LKL, Garrido MI.* ***Sensory prediction errors in the continuum of psychosis****. Schizophr Res. 2017 Apr 27. pii: S0920-9964(17)30206-2.* *2: Griffin JD, Fletcher PC.* ***Predictive Processing, Source Monitoring, and Psychosis****. Annu Rev Clin Psychol. 2017 May 8;13:265-289.* *3: Corlett PR.* ***I Predict, Therefore I Am: Perturbed Predictive Coding Under Ketamine and in Schizophrenia****. Biol Psychiatry. 2017 Mar 15;81(6):465-466.* *4: Tschacher W, Giersch A, Friston K.* ***Embodiment and Schizophrenia: A Review of Implications and Applications****. Schizophr Bull. 2017 Mar 3.* *5: van Schalkwyk GI, Volkmar FR, Corlett PR.* ***A Predictive Coding Account of Psychotic Symptoms in Autism Spectrum Disorder****. J Autism Dev Disord. 2017 May;47(5):1323-1340.* *6: Schmack K, Rothkirch M, Priller J, Sterzer P.* ***Enhanced predictive signalling in schizophrenia****. Hum Brain Mapp. 2017 Apr;38(4):1767-1779.* *7: Sterzer P, Mishara AL, Voss M, Heinz A.* ***Thought Insertion as a Self-Disturbance: An Integration of Predictive Coding and Phenomenological Approaches****. Front Hum Neurosci. 2016 Oct 12;10:502. eCollection 2016.* *8: Kort NS, Ford JM, Roach BJ, Gunduz-Bruce H, Krystal JH, Jaeger J, Reinhart RM, Mathalon DH.* ***Role of N-Methyl-D-Aspartate Receptors in Action-Based Predictive Coding Deficits in Schizophrenia****. Biol Psychiatry. 2017 Mar 15;81(6):514-524.* *9: Friston K, Brown HR, Siemerkus J, Stephan KE.* ***The dysconnection hypothesis (2016)****. Schizophr Res. 2016 Oct;176(2-3):83-94.* *10: Roa Romero Y, Keil J, Balz J, Gallinat J, Senkowski D.* ***Reduced frontal theta oscillations indicate altered crossmodal prediction error processing in schizophrenia****. J Neurophysiol. 2016 Sep 1;116(3):1396-407.* *11: Adams RA, Bauer M, Pinotsis D, Friston KJ.* ***Dynamic causal modelling of eye movements during pursuit: Confirming precision-encoding in V1 using MEG****. Neuroimage. 2016 May 15;132:175-89.* *12: Wacongne C.* ***A predictive coding account of MMN reduction in schizophrenia****. Biol Psychol. 2016 Apr;116:68-74.* *13: Powers AR 3rd, Gancsos MG, Finn ES, Morgan PT, Corlett PR.* ***Ketamine-Induced Hallucinations. Psychopathology****. 2015;48(6):376-85.* *14: Adams RA, Huys QJ, Roiser JP.* ***Computational Psychiatry: towards a mathematically informed understanding of mental illness****. J Neurol Neurosurg Psychiatry. 2016 Jan;87(1):53-63.* *15: Rentzsch J, Shen C, Jockers-Scherübl MC, Gallinat J, Neuhaus AH.* ***Auditory mismatch negativity and repetition suppression deficits in schizophrenia explained by irregular computation of prediction error****. PLoS One. 2015 May 8;10(5):e0126775.* *16: Castelnovo A, Ferrarelli F, D'Agostino A.* ***Schizophrenia: from neurophysiological abnormalities to clinical symptoms****. Front Psychol. 2015 Apr 20;6:478.* *17: Notredame CE, Pins D, Deneve S, Jardri R. What* ***visual illusions teach us about***

	***schizophrenia**. Front Integr Neurosci. 2014 Aug 12;8:63.* *18: Moran RJ, Jones MW, Blockeel AJ, Adams RA, Stephan KE, Friston KJ. **Losing control under ketamine: suppressed cortico-hippocampal drive following acute ketamine in rats**. Neuropsychopharmacology. 2015 Jan;40(2):268-77.* *19: Fogelson N, Litvak V, Peled A, Fernandez-del-Olmo M, Friston K. **The functional anatomy of schizophrenia: A dynamic causal modeling study of predictive coding**. Schizophr Res. 2014 Sep;158(1-3):204-12.* *20: Horga G, Schatz KC, Abi-Dargham A, Peterson BS. **Deficits in predictive coding underlie hallucinations in schizophrenia**. J Neurosci. 2014 Jun 11;34(24):8072-82.* *21: Jardri R, Denève S. **Circular inferences in schizophrenia**. Brain. 2013 Nov;136(Pt 11):3227-41.* *22: Ford JM, Palzes VA, Roach BJ, Mathalon DH. **Did I do that? Abnormal predictive processes in schizophrenia when button pressing to deliver a tone**. Schizophr Bull. 2014 Jul;40(4):804-12.* *23: Adams RA, Stephan KE, Brown HR, Frith CD, Friston KJ. **The computational anatomy of psychosis. Front Psychiatry**. 2013 May 30;4:47.* *24: Nazimek JM, Hunter MD, Woodruff PW. Auditory **hallucinations: expectation-perception model**. Med Hypotheses. 2012 Jun;78(6):802-10.* *25: Lalanne L, van Assche M, Giersch A. **When predictive mechanisms go wrong: disordered visual synchrony thresholds in schizophrenia**. Schizophr Bull. 2012 May;38(3):506-13.* *26: Strelnikov K. **Can mismatch negativity be linked to synaptic processes? A glutamatergic approach to deviance detection**. Brain Cogn. 2007 Dec;65(3):244-51.*
Precision, predictive coding and Bayesian inference in **autism and autistic spectrum disorder**	*1: van Schalkwyk GI, Volkmar FR, Corlett PR. **A Predictive Coding Account of Psychotic Symptoms in Autism Spectrum Disorder**. J Autism Dev Disord. 2017 May;47(5):1323-1340.* *2: Seth AK, Friston KJ. **Active interoceptive inference and the emotional brain**. Philos Trans R Soc Lond B Biol Sci. 2016 Nov 19;371(1708). pii: 20160007.* *3: Van de Cruys S, Van der Hallen R, Wagemans J. **Disentangling signal and noise in autism spectrum disorder**. Brain Cogn. 2017 Mar;112:78-83.* *4: Manning C, Kilner J, Neil L, Karaminis T, Pellicano E. **Children on the autism spectrum update their behaviour in response to a volatile environment**. Dev Sci. 2016 Aug 6. doi: 10.1111/desc.12435.* *5: Chan JS, Langer A, Kaiser J. **Temporal integration of multisensory stimuli in autism spectrum disorder: a predictive coding perspective**. J Neural Transm (Vienna). 2016 Aug;123(8):917-23.* *6: von der Lühe T, Manera V, Barisic I, Becchio C, Vogeley K, Schilbach L. **Interpersonal predictive coding, not action perception, is impaired in autism**. Philos Trans R Soc Lond B Biol Sci. 2016 May 5;371(1693).* *7: Gonzalez-Gadea ML, Chennu S, Bekinschtein TA, Rattazzi A, Beraudi A, Tripicchio P, Moyano B, Soffita Y, Steinberg L, Adolfi F, Sigman M, Marino J, Manes F, Ibanez A. **Predictive coding in autism spectrum disorder and attention deficit hyperactivity disorder**. J Neurophysiol. 2015 Nov;114(5):2625-36.* *8: Brewer R, Happé F, Cook R, Bird G. **Commentary on "Autism, oxytocin and interoception": Alexithymia, not Autism Spectrum Disorders, is the consequence of interoceptive failure**. Neurosci Biobehav Rev. 2015 Sep;56:348-53.* *9: Palmer CJ, Seth AK, Hohwy J. **The felt presence of other minds: Predictive processing, counterfactual predictions, and mentalising in autism**. Conscious Cogn. 2015 Nov;36:376-89. doi: 10.1016/j.concog.2015.04.007. Epub 2015 Apr 28. Review. PubMed PMID: 25934216.*
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Precision, predictive coding and Bayesian inference in **hallucinations and hallucinosis**	*1: Erickson MA, Albrecht M, Ruffle A, Fleming L, Corlett P, Gold J.* ***No association between symptom severity and MMN impairment in schizophrenia: A meta-analytic approach****. Schizophr Res Cogn. 2017 May 18;9:13-17.* *2: Powers AR III, Kelley M, Corlett PR.* ***Hallucinations as top-down effects on perception****. Biol Psychiatry Cogn Neurosci Neuroimaging. 2016 Sep;1(5):393-400.* *3: Griffin JD, Fletcher PC.* ***Predictive Processing, Source Monitoring, and Psychosis****. Annu Rev Clin Psychol. 2017 May 8;13:265-289.* *4: van Schalkwyk GI, Volkmar FR, Corlett PR.* ***A Predictive Coding Account of Psychotic Symptoms in Autism Spectrum Disorder****. J Autism Dev Disord. 2017 May;47(5):1323-1340.* *5: Schmack K, Rothkirch M, Priller J, Sterzer P.* ***Enhanced predictive signalling in schizophrenia****. Hum Brain Mapp. 2017 Apr;38(4):1767-1779.* *6: Sterzer P, Mishara AL, Voss M, Heinz A.* ***Thought Insertion as a Self-Disturbance: An Integration of Predictive Coding and Phenomenological Approaches****. Front Hum Neurosci. 2016 Oct 12;10:502.* *7: Roa Romero Y, Keil J, Balz J, Gallinat J, Senkowski D.* ***Reduced frontal theta oscillations indicate altered crossmodal prediction error processing in schizophrenia****. J Neurophysiol. 2016 Sep 1;116(3):1396-407.* *8: Teufel C, Subramaniam N, Dobler V, Perez J, Finnemann J, Mehta PR, Goodyer IM, Fletcher PC. Shift toward prior knowledge confers a perceptual advantage in early psychosis and psychosis-prone healthy individuals. Proc Natl Acad Sci U S A. 2015 Oct 27;112(43):13401-6.* *9: Powers AR 3rd, Gancsos MG, Finn ES, Morgan PT, Corlett PR. Ketamine-Induced Hallucinations. Psychopathology. 2015;48(6):376-85.*

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