BRAIN COMMUNICATIONS

SCIENTIFIC COMMENTARY

Unilateral neglect within the predictive processing framework

This scientific commentary refers to 'Deficits of hierarchical predictive coding in left spatial neglect', by Doricchi et al. (https://doi.org/10.1093/braincomms/fcab111).

Patients with the unilateral neglect syndrome fail to notice and act upon salient stimuli contralateral to the side of their lesion, independent of sensory deficit, and frequently without any awareness of their deficit (anosognosia).[1] Despite the fact that the syndrome is a highly frequent sequel of right hemisphere damage, and has grave consequences for patients' rehabilitation, the underlying mechanism has puzzled researchers for decades, with theories pointing to faulty attention circuits, neural spatial representations, interhemispheric balance and others. Recently, the predictive coding framework has emerged as an explanatory model of brain and behaviour, from perception to action.[2] Could this model explain the deficits seen in Neglect?

Predictive coding

The predictive coding framework postulates that perception is an active process—the brain does not simply register and process information, but rather makes inferences about the most probable causes of incoming sensory data, using top-down predictions, or 'priors' in Bayesian terms.[2,3] According to this principle, bottom-up information is not the input itself, but the mismatch between what is predicted and what actually happens ('prediction error', PE). This is implemented in a hierarchical manner, such that every level in the hierarchy makes predictions about, and reads prediction errors from, the level below (Fig. 1C and D). The mismatch negativity (MMN) event-related potential is thought to be an early neural signature of local sensory, task-irrelevant PE,[4] while the later P3 response shows sensitivity to violations of a higher level regularity, at a longer time scale[5] and beyond the sensory cortex.[6]

Being (un)aware of local change

In a new study in *Brain Communications*, Doricchi et al.[7] probed unilateral neglect patients' early and late PE signals using a variant of the 'global-local' paradigm.[5,8,9] The backbone of this paradigm is a pattern of 5 sequential tones. In the critical conditions, 4 identical tones (local 'standards') are followed by one local 'deviant' tone. This deviant forms a local change relative to the preceding standards, and is expected to elicit an MMN response. When this 4-1 pattern repeats again and again, it forms a global regularity, where the local deviant can be expected. In this situation, occasionally replacing the deviant by a different one, or even replacing the deviant with a standard, violates this global regularity, which should elicit a P3 response. In the critical conditions of the new study, the standards were presented at the midline (M), whereas the local deviants could be either on the left (L), the right (R), or altogether omitted (Fig. 1A). A novel aspect of the design was that the global regularity was established in different blocks of trials by either a 'frequent left' (MMMML) or a 'frequent right' (MMMMR) pattern (70% of the times), and this regularity was violated by rare (20%) 4-1 patterns including a right deviant (MMMMR), or a left deviant (MMMML), respectively. In both cases, rare patterns with an omitted last tone (MMMM_) were also included (with 10% probability). This design allowed Dorrichi et al.[7] to probe both responses to local changes (whether frequent or not), resulting in 'local PE', and the formation and violation of global regularities, resulting in a 'global PE'.

Previous EEG studies have shown that patients with Neglect, despite normal hearing, do not elicit a typical MMN response to a deviant tone on their neglected (left) side, especially when the deviation is in the spatial location of the stimuli.[10,11] This finding is conceptually replicated in the new study[7] when considering left and right local deviants. Whether *left* side deviant tones were globally frequent or globally rare, no MMN was observed in the patients. In contrast, the patients evinced a typical MMN to *right* side local deviant tones, whether globally rare or globally frequent.

Being (un)aware of global violations

An intriguing result in the new study pertains to the P3 (late PE), the putative

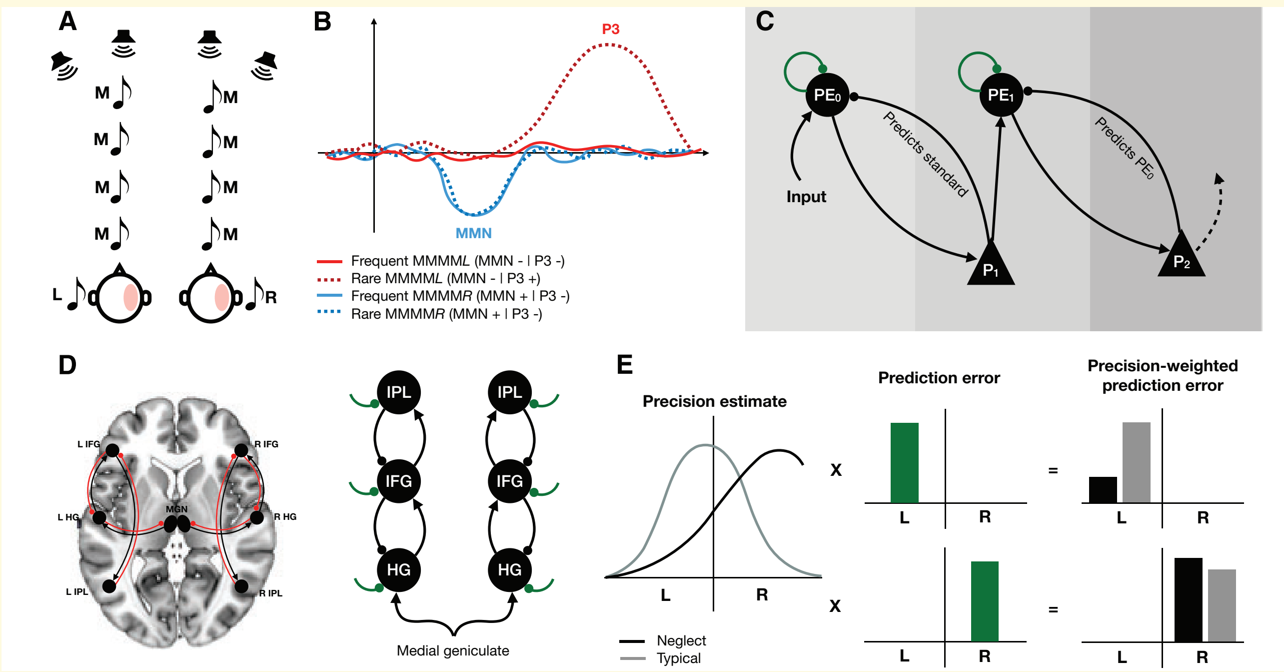

Figure 1 Reduced precision estimate in unilateral neglect? (**A**) In the main contrast in Dorrichi et al.'s study,[7] quintets of stimuli were the building block of a sequence. Each quintet presented 4 sequential tones from a midline location ('local standards'), followed by either a left or right lateralized tone ('local deviant'). In a given block, either the left or right penultimate tone was frequent ('global standard'), while the other was rare ('global deviant'). Pink blob on the schematic heads signals the side of the brain lesion in patients. (**B**) Schematic depiction of the results in patients with left unilateral neglect. Right but not left local deviants elicited an MMN response, Left global deviants elicited a P3 response (in the context of right global standards), but right global deviants (in the context of left global standards) did not. (**C**) A schematic diagram of hierarchical predictive coding system. PE_0—Low level prediction error, PE_1—prediction error at the next level, P_1, P_2—prediction neurons. Under normal circumstances, P_1 predicts the stimulus is a local standard, thus the local deviant produces a net activation at PE_0, which P_2 has learned to predict. PE_1 is putatively associated with the MMN, while PE_2 is associated with P3 in this simplified model. The green connections represent a gain-control device associated with precision estimate of the PE. (**D**) Schematic diagram of the predictive network for auditory sequences (adapted from Dietz et al.[11]) (**E**) Typically, precision estimate is maximal for midline sounds (possibly with a small bias to the left). In patients, it is strongly biased towards the right side of space. Precision-weighted PEs in patients are thus strongly reduced for left sided but slightly enhanced for right local deviants.

signature of global regularity violation detection. When the global regularity was established by a 'frequent right' deviant (i.e. 70% MMMMR patterns), a violation by a rare pattern including a left deviant (i.e. 20% MMMML patterns) elicited a P3 in the patients. As noted above, that same stimulus did not elicit a local MMN, and yet elicited a later P3 response. In contrast, no P3 was elicited when the 'frequent left' deviant pattern formed the global regularity (i.e. 70% MMMML), and violation was due to a rare (20%) MMMMR sequence, even though the latter stimulus did elicit an MMN response. This forms an apparent double dissociation between change detection (local PE) and detection of higher level pattern violation (global PE): the right side deviants that elicit an MMN do not elicit a P3, and even more remarkably, left side deviants that do not elicit an early MMN, do elicit a later P3 (Fig. 1B). How is that possible? The answer may arise naturally from the predictive coding framework.

A predictive processing account of unilateral neglect?

PE neurons in superficial cortical layers are conceived as performing a subtraction between the bottom-up input and top-down predictions[2,3] (Fig. 1C). Bottom-up PE signals, in turn, modify (update) the top-down predictions, so as to minimize ensuing PE. In this way, predictions eventually come to match the input, and validly reflect the external environment. An important addition to this basic circuit is the notion that the impact of the PE neurons on predictions can be gain-modulated (weighted) based on an estimate of its precision (the inverse of variability). In other words, predictions are modulated by precision-weighted prediction errors, so that only reliable PEs are allowed to modify the predictions. This gain, or precision weighting, mechanism may be seen as equivalent to attention control.[12,13]

With this picture in mind, let's consider Dorrichi et al.'s[7] double dissociation with the hypothesis that the 'precision weight' of left oriented PE neurons is low (Fig. 1E). With low precision weight on the left sensorium, PEs are suppressed. Hence, there is no MMN for the final left side tone (L) in MMMML, whether this pattern is frequent or rare. Moreover, with no PEs generated by the final left deviant, global prediction for the frequent pattern MMMML will not be formed, as higher level prediction update depends on input from lower level precision-weighted PE neurons. Seen from the top, a global prediction for the pattern MMMML involves expecting a local PE (MMN) at the fifth tone at the lower level.[9] This explains the absence of P3 to rare MMMMR patterns, or to omissions that violate the frequent MMMML pattern. Now let us turn to what happens when the frequent pattern is MMMNR. Firstly, the final right deviant elicits a typical local PE (MMN), as the precision weighting is high. Secondly, a global regularity is formed based on this high precision-weighted local PE to right deviants. When a rare MMMML is presented in this context, the expected local PE is lacking, as noted already, because of the low precision weighting on the left side of the sensorium, hence no MMN is seen. In contrast, the P3 emerges as a signature of global violation, which results from an effective omission of the *expected* right PE. Thus, the observed double dissociation could be explained by assuming low precision weighting of left side inputs, possibly related to altered fronto-parietal connectivity in the damaged right hemisphere.[11] In addition, assuming the precision weighting for right PEs is abnormally high in Neglect patients, may also explain why an omission response was generated in patients with Neglect in the context of frequent MMMMR patterns, but not in other patients or controls[7]. However, considering that an omission response was elicited only in this case, and not for example in healthy controls, the latter hypothesis requires further investigation.

The MMN is frequently seen as a 'preattentive' response, because it is elicited in situations in which the subjects' attention is diverted and there are no task demands. Reduced MMN responses to left deviants in Neglect suggests that patients may also suffer from a deficit in a process that is independent of attention,[10] which is contrary to theories that see Neglect as an attentional deficit. Within the predictive coding framework, however, the distinction between pre-attentive and attentive becomes blurred. A low precision weight, conceived as a form of gain-control or attention, hinders the generation of PE to left-sided stimuli, thus also hindering the updating of top-down predictions about left-sided stimuli. Under the contentious premise that high level predictions form the basis for the content of conscious awareness,[14] this may explain the core deficit of Neglect patients, which is lack of conscious awareness of the left side of space.

Acknowledgement

The authors thank Chen Gueta for production of the figure.

Data availability

Data sharing is not applicable to this article as no new data were created or analysed.

Funding

L.Y.D. is supported by the Jack H Skirball research fund and the Israeli Science Foundation grant 3504/20.

Competing interests

The authors report no competing interests.

Marta I. Garrido[1,]* *and*
Leon Y. Deouell[2,3]*
[1]*Melbourne School of Psychological Sciences, The University of Melbourne, Melbourne, Australia*
[2]*The Edmond and Lily Safra Center for Brain Sciences, Jerusalem, Israel*
[3]*Department of Psychology, The Hebrew University of Jerusalem, Jerusalem, Israel*

These authors contributed equally to this work.

Correspondence to: Leon Y. Deouell,
The Edmond and Lily Safra Center for Brain Sciences, Jerusalem, Israel.
E-mail:leon.deouell@mail.huji.ac.il

doi:10.1093/braincomms/fcab193

References

1. Parton A, Malhotra P, Husain M. Hemispatial neglect. J Neurol Neurosurg Psychiatry. 2004;75(1):13–21.
2. Clark A. Whatever next? Predictive brains, situated agents, and the future of cognitive science. Behav Brain Sci. 2013; 36(3):181–204.
3. Friston K. A theory of cortical responses. Philos Trans R Soc Lond B Biol Sci. 2005;360(1456):815–836.
4. Garrido MI, Kilner JM, Stephan KE, Friston KJ. The mismatch negativity: A review of underlying mechanisms. Clin Neurophysiol. 2009;120(3):453–463.
5. Bekinschtein TA, Dehaene S, Rohaut B, Tadel F, Cohen L, Naccache L. Neural signature of the conscious processing of auditory regularities. Proc Natl Acad Sci U S A. 2009;106(5):1672–1677.
6. Durschmid S, Edwards E, Reichert C et al. Hierarchy of prediction errors for auditory events in human temporal and frontal cortex. Proc Natl Acad Sci U S A. 2016;113(24):6755–6760. [10.1073/pnas.1525030113]
7. Doricchi F, Pinto M, Pellegrino M, et al. Deficits of hierarchical predictive coding in left spatial neglect. Brain Commun. 2021;3(2):fcab111.
8. Wacongne C, Labyt E, van Wassenhove V, Bekinschtein T, Naccache L, Dehaene S. Evidence for a hierarchy of predictions and prediction errors in human cortex. Proc Natl Acad Sci U S A. 2011;108(51): 20754–20759.
9. Chao ZC, Takaura K, Wang L, Fujii N, Dehaene S. Large-scale cortical networks for hierarchical prediction and prediction error in the primate brain. Neuron. 2018;100(5):1252–1266.e3.
10. Deouell LY, Bentin S, Soroker N. Electrophysiological evidence for an early(pre-attentive) information processing deficit in patients with right hemisphere damage and unilateral neglect. Brain. 2000;123 (Pt 2):353–365.

11. Dietz MJ, Nielsen JF, Roepstorff A, Garrido MI. Reduced effective connectivity between right parietal and inferior frontal cortex during audiospatial perception in neglect patients with a right-hemisphere lesion. Heart Res. 2021;399: 108052.
12. Hohwy J. Attention and conscious perception in the hypothesis testing brain. Hypothesis and Theory. Front Psychol. 2012;3:96.
13. Friston K. The free-energy principle: A rough guide to the brain? Trends Cogn Sci. 2009;13(7):293–301.
14. Hohwy J, Seth A. Predictive processing as a systematic basis for identifying the neural correlates of consciousness. Philos Mind Sci. 2020;1(II):doi:10.33735/phimisci.2020.II.64.