BRAIN UPDATE

Evidence and implications of abnormal predictive coding in dementia

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The diversity of cognitive deficits and neuropathological processes associated with dementias has encouraged divergence in pathophysiological explanations of disease. Here, we review an alternative framework that emphasizes convergent critical features of cognitive pathophysiology. Rather than the loss of 'memory centres' or 'language centres', or singular neurotransmitter systems, cognitive deficits are interpreted in terms of aberrant predictive coding in hierarchical neural networks.

This builds on advances in normative accounts of brain function, specifically the Bayesian integration of beliefs and sensory evidence in which hierarchical predictions and prediction errors underlie memory, perception, speech and behaviour. We describe how analogous impairments in predictive coding in parallel neurocognitive systems can generate diverse clinical phenomena, including the characteristics of dementias.

The review presents evidence from behavioural and neurophysiological studies of perception, language, memory and decision-making. The reformulation of cognitive deficits in terms of predictive coding has several advantages. It brings diverse clinical phenomena into a common framework; it aligns cognitive and movement disorders; and it makes specific predictions on cognitive physiology that support translational and experimental medicine studies. The insights into complex human cognitive disorders from the predictive coding framework may therefore also inform future therapeutic strategies.

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Introduction

Cognitive deficits in neurodegenerative diseases have often been characterized as the loss of core functional modules in distinct brain regions, or specific networks, each serving functionally specialized cognitive systems such as memory, language comprehension or executive function. This approach emphasizes the functional differences between disorders linked to functional anatomical susceptibility and network vulnerability.[1] Alongside these functional anatomical differences that contribute to distinct phenotypes, preclinical models and clinical studies suggest convergence in important aspects of the pathophysiology of different dementias, with commonalities for example in terms of loss of synapses, synaptic plasticity and major neurotransmitters.[2] The

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relative contributions of toxic misfolded protein aggregates, neuroinflammation and proteostasis to synaptic impairment vary across dementias, but their physiological consequences overlap, with potential convergence on a core cognitive mechanisms of predictive coding. Here we propose a re-evaluation of the diversity of cognitive features in dementia, in terms of impairments in predictive coding, leading to a trans-diagnostic neuro-computational model that may aid the development of novel therapeutic strategies.

Predictive coding is a core feature of brain function, implementing generative models that 'explain' sensory inputs via hierarchical beliefs about the world.[3–6] In this review, we reassess clinical deficits in terms of the disruption of predictive coding in precisely tuned neural hierarchies engaged in prediction, prediction error and inference. The predictive coding account of normative brain function integrates cognitive and computational neuroscience to explain perception and action. The central tenet is that the brain acts as an active inference machine that learns statistical regularities of the external world (Box 1) and generates predictions to increase the efficiency of information processing and understanding of the sensorium.[3–6]

The predictive coding account provides a common neurobiological framework to describe diverse cognitive, perceptual and behavioural phenomena. For example, there is evidence for predictive coding in vision,[45,46] rhythm perception,[47,48] auditory processing,[49–53] reward and preferences[54] and action control.[55,56] The representation of predictions, prediction errors and precision in each system depends on a fine-tuned cortical hierarchy, with laminar-specific connectivity and balanced excitatory-inhibitory neurochemistry (Fig. 1A). Deficits in predictive coding have been proposed to cause domain-specific and domain-general cognitive impairments in neuropsychiatric disorders as diverse as psychosis,[57,58] autism[59,60] and alien limb.[61]

We propose that dementias' effects on memory, perception, language and action control may also arise from a change in predictive coding. In particular, we set out how the effect of neurodegeneration on the 'precision' of predictions and prediction error can impair perception, learning and complex behaviours. The symptoms arising from a change in predictive coding are a function of the neural networks that are selectively vulnerable to each specific molecular pathology. The predictive coding account of dementia is therefore not an alternative to network specificity models,[1] but instead augments these models by describing the homologous changes in predictive coding arising within each network.

We start with the basic processes of perception and action to introduce the principles predictive coding and the direct evidence is strongest. We then consider higher cognitive disorders, of amnesia and aphasia, and neuropharmacological factors, with examples drawn from studies of Alzheimer's disease, Parkinson's disease, frontotemporal dementia and dementia with Lewy bodies.

Perception

In perceiving our environment, one makes use of prior knowledge and context to predict sensory inputs. For example, in a complex auditory scene such as a noisy cocktail party, prior knowledge or experience facilitates the parsing of constituent objects (or speakers) in time and space, making it easy to recognize one's own name ('the cocktail party effect').[62] Top-down predictions based on prior experience of the speakers, their language and the topic, facilitate this segregation.[63] In vision, context-based predictions likewise aid rapid object recognition under both normal and challenging conditions.[4,64] The use of auditory predictions is largely preserved in normal ageing. Indeed, people may become more dependent on their predictions and perceptually less sensitive to the sensorium with age, as the precision of the higher-order prediction errors increases relative to the precision sensory evidence.[14,28]

This balance is disrupted in mild cognitive impairment and dementia, with degeneration of temporo-parietal cortex from Alzheimer's disease.[65] Accordingly, patients develop greater difficulty following conversations in the presence of background noise, show impairments in segregating, tracking and grouping auditory objects that evolve over time[66] and in perceiving sound location

Box 1 Predictive coding and hierarchical networks

Predictive coding is a process by which the brain updates a model of the environment, to explain sensory inputs. The process applies hierarchically over increasingly abstract causes, and over time, forming the basis of diverse cognitive and behavioural functions. It rests the premise that perception is a probabilistic inference. Complex and abstract beliefs are represented in higher levels (e.g. on semantics and social norms) and direct sensory inputs at lower levels. Based on learned statistical dependencies, each level predicts the activity in the level below ('feedback'). A mismatch between the prediction and the sensory input leads to a prediction error, which is propagated back up the hierarchy ('feedforward'). The forward and backward connections convey prediction errors and predictions, respectively.[7,8]

Different biological implementations of predictive coding have been put forward at micro- and macroscopic levels,[3–6] but they have multi-level hierarchies of neural circuits in common. There are different algorithmic implementations of the way in which the fit between predictions and sensory data is optimized, and the underlying model updated (e.g. linear estimation of parameters,[6] Bayesian inference,[9] a review of models).[10] There are also alternatives to predictive coding, that nonetheless posit that the brain performs a probabilistic inference in hierarchical networks, and maintains a generative (i.e. explanatory) model of the environment by alternative mechanisms.[11] This review does not seek to differentiate these alternative mechanisms, but focus on their commonalities, with the generation of predictions and updating them in response to prediction errors.

A critical feature of predictive coding is the estimation of uncertainty of the predictions and sensory inputs. Both the predictions and prediction errors are relayed with varying 'precision' (i.e. the inverse of variance, or uncertainty). This precision determines the relative weighting of the prediction error, whilst priors are updated iteratively, across all levels of the hierarchy.[12,13] Precision weighting of the prediction errors is controlled by neuromodulation (Box 2) and postsynaptic gain control at the cellular level. Feedforward propagation of more precise prediction errors will have a greater impact updating beliefs represented in the higher levels (i.e. faster learning). Feedback generation of more precise predictions 'cancels out' incoming prediction errors, leading to stable beliefs and behaviour (i.e. slow learning). Healthy cognition requires fine tuning of this process, adjusting relative precision at upper versus lower levels of the hierarchy. The impact of neurodegeneration on the neural mechanisms that regulate precision, and govern the representations within each level, explain diverse cognitive and behavioural phenomena in dementia, and raise new hypotheses about candidate treatment strategies.

Box 2 Precision changes in dementia and neurotransmitters

'Precision' represents the level of certainty, and describes the confidence attributed to prediction errors at each level of the cortical hierarchy.[3,5] For example, in noisy settings with high levels of uncertainty (e.g. driving on a foggy day, talking during a concert), precision of the sensory prediction errors is reduced while the precision at the higher levels is relatively increased. Neurotransmitters such as acetylcholine,[14–18] glutamate,[19–21] GABA[22–27] and norepinephrine[18] have been shown to regulate prediction errors and their precision across different cortical hierarchies. Impairments in the neurotransmitter mediated precision weighting gives rise to diverse clinical representations in dementia depending on the level and the functional domain of the cortical hierarchy where the mechanistic impairment occurs.

An example of the abnormally high precision in the lower levels of the hierarchy comes from Parkinsonian disorders. Akinesia, the poverty of movement, can arise from reduced precision in the higher order sensorimotor prediction errors, and an over-reliance on sensory evidence (Fig. 1D).[12,28] Akinesia can be partially improved using the peripheral vibration devices that increase the uncertainty of sensory evidence, thereby reducing the precision.[29,30] However precision changes are more commonly observed at the higher levels of the hierarchy. In normal ageing, impairments in vision and hearing, lead to the adaptation of precision weights across the cortical hierarchy,[31] where the reliance on 'inaccurate' sensory evidence is reduced, and to balance, precision at higher cortical levels are boosted. Similarly, in Parkinson's disease and Lewy body dementia, in the visual cortical hierarchy, the precision at the higher level prediction errors are up-weighted, albeit abnormally, giving rise to visual hallucinations.[32–36]

A key modulator of precision is acetylcholine that suppresses prediction errors at the higher order and regulates precision of the sensory prediction errors.[14–17] Cholinergic loss can affect ascending sensory precision even in the absence of atrophy. Impaired mismatch negativity responses in Alzheimer's disease, indicating unsuccessful sensory learning, is partially explained by the widespread degeneration of cholinergic projections.[37,38] Similarly, patients with Lewy body dementia who have more severe degeneration of their cholinergic pathways experience more visual hallucinations.[39–41] Cholinesterase inhibitors that mediate sensory precision, can amplify the amplitude of the mismatch response in patients with Alzheimer's disease,[42] and alleviate hallucinations in Lewy body dementia.[43] Acetylcholine regulates inhibitory activity by suppressing or inactivating GABAergic interneurons.[25–27] While slower neurotransmitters like acetylcholine are proposed to compute the precision, faster neurotransmitters like GABA are thought to encode the prediction errors.[44] Patients with behavioural variant frontotemporal dementia show reduced mismatch negativity response, as a product of impaired inhibitory connections and reduced GABA concentrations in the frontal cortex.[23,24] These patients show reduced precision in higher levels of the auditory hierarchy, leading to errors in encoding of conditional expectations at lower levels.[22]

and motion.[65] They become worse even at automatic prediction of repetitive stimuli and fail to generate a prediction error following unexpected sensory events. This failure to generate a prediction error with Alzheimer's disease and other dementias is readily seen in the reduced 'mismatch negativity responses' in oddball tasks.[37,67–69] Alzheimer's disease similarly impairs higher order precepts such as melodic contours.[70] Even otherwise healthy *APOE4* carriers (i.e. at an elevated risk of developing Alzheimer's disease) show impairments in detecting auditory targets using contextual information.[71]

In the visual domain, hallucinations and illusions commonly occur with cortical Lewy body pathology, in Parkinson's disease dementia and dementia with Lewy bodies. The perceptual content is commonly influenced by the immediate environment or autobiographical memories, with pareidolic experiences in ambiguous scenes,[72] or the perception of familiar people or pets even if known to have died.[73] The hallucinations are typically visually complex and familiar.[14,15,74] This can be understood as a result of abnormal up-weighting of beliefs (i.e. more precise priors) that establish overly precise predictions relative to down-weighting (i.e. less precise) visual sensory evidence.[32–34,58] Note that it is not just the absolute precision that matters, but the relative precision between upper and lower levels in a hierarchy. Note too that the symptoms depend on the anatomical distribution of the network that represents the cognitive hierarchy. The medial temporal and medial prefrontal areas are implicated in the cognitive hierarchy for such misperceptions,[75] with hallucinations associated with abnormal activity and connectivity among lower visual cortical regions.[35,76–83] The loss of cholinergic modulation of the precision of neural representations is a candidate cause, even in the absence of significant atrophy. Such cholinergic loss reduces the precision of feed-forward prediction errors relative to the precision of feedback predictions from higher level priors.[14–17] This accords with the observation that patients who have more severe degeneration of their cholinergic pathways experience more visual hallucinations,[39–41] and symptoms are alleviated with cholinesterase inhibitors.[43]

Action, apathy and behavioural disorder

As Adams *et al.*[84] highlight, perceptual and motor systems are not separate entities, but operate as a single 'inference machine' that serves to predict sensory input in all sensory domains and intermediate inferences on the causes of the sensory inputs. The concept of 'active inference' posits that prediction errors can be reduced by actively changing sensory inputs through movement. Active inference uses hierarchical predictive coding, with direct evidence coming from the physiology of motor control (Fig. 1A).[56]

The failure to attenuate proprioceptive prediction errors in the lower levels of a behavioural hierarchy leads to akinesia (Fig. 1D),[85] in the context of neurodegenerative movement disorders like Parkinson's disease. Over-precise priors (in upper levels of a motor control hierarchy, represented by premotor and prefrontal cortex) also explain the alien limb syndrome (that one's own limb is moving without intention or volition). Specifically, alien limb syndrome is associated with disrupted information flow between medial areas (supplementary motor area) that encode precision of proprioceptive predictions to the lateral pre-motor areas which encode action outcomes.[61]

There is empirical evidence for active inference at the lower level of the cognitive hierarchy for behaviour, expressed as specific actions. For example, there is ubiquitous 'sensorimotor attenuation' in health across the lifespan: a transient down-weighting of the predicted sensory consequences of actions, observed in 98% of healthy adults (Fig. 1B).[31] Attenuation facilitates movement and provides a sense of agency.[86] In healthy ageing, there is greater reliance on predictions arising from greater precision of prior beliefs,

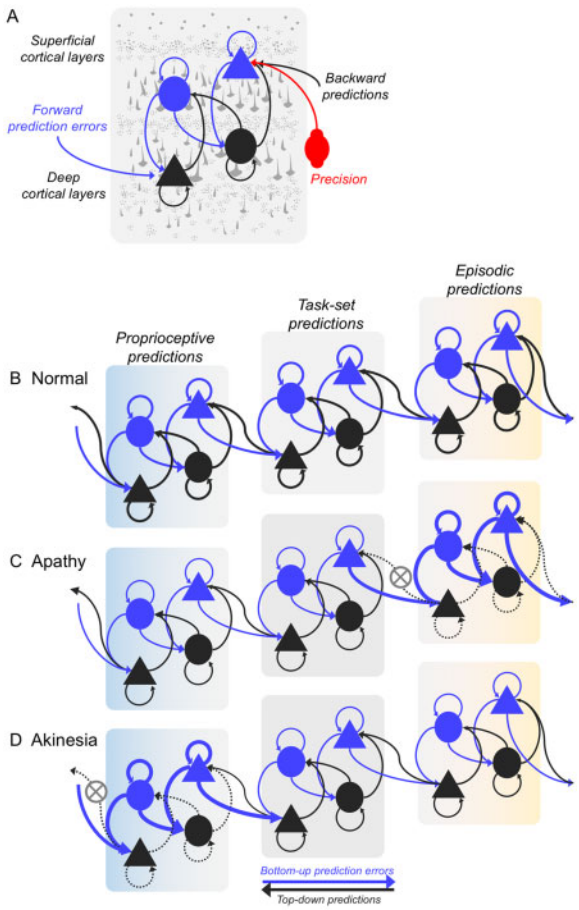

Figure 1 Predictive coding mechanism within the hierarchical brain network. (**A**) Schematic illustration of the predictive coding mechanism in a single cortical region at one layer in the hierarchy. Top-down predictions are conveyed via the backward connections (black arrows) from state representation units (black nodes) in deep cortical layers. The predictions are compared with conditional expectations at the lower level in the hierarchy by the error units in the superficial cortical layers (blue nodes) to produce prediction errors, which are passed bottom-up (blue arrows) to the higher level to update the predictions. Triangles and circles represent pyramidal neurons and inhibitory interneurons respectively. Precision weighting (red) regulates the postsynaptic gain of the error units, e.g. via neuromodulation. Panels **B–D** illustrate three layers of a hierarchical network of the behavioural/motor system, with three cortical layers from *left* (light blue) to *right* (yellow). Each layer of the hierarchy makes predictions relayed in a top-down fashion. Higher layers of the network make episodic predictions that are multimodal, abstract and span across a longer timescale (e.g. 'that the city marathon is happening'). Intermediate layers represent medium-term, task-set or context specific predictions (e.g. 'I am running, and see supporters and water stands'). Lower layers make transient, proprioceptive predictions on the immediate consequences of running action (e.g. 'position of my limbs'). (**B**) Healthy state of the hierarchy with optimal control in which top-down predictions are matched by sensory inputs, minimizing prediction errors at each layer. In apathy and akinesia, behavioural impairments arise from a mismatch between the strength of predictions and prediction errors. (**C**) In apathy, top-down predictions at the higher level are represented with insufficient precision, and are therefore overwhelmed by bottom-up prediction errors from the intermediate hierarchical level. Therefore, high-level priors, representing abstract goals and desires, fail to be translated into specific proprioceptive predictions for movement, and as such there is a loss of goal-directed behaviour. (**D**) In contrast, with akinesia there is a poverty of movement because predictions at the lowest hierarchical level fail to suppress proprioceptive prediction errors. Even though the absence of behaviour may manifest similarly in apathy and akinesia, the underlying mechanism of impairment arises from predictive mismatch in different levels of the hierarchical network.

and less on the sensorium.[31] In neurodegenerative parkinsonism, deficits in sensorimotor predictions (reduced precision) results in an over-reliance on sensory evidence and poverty of movement.[12,28] Such deficits in sensorimotor predictions are linked to disease severity of corticobasal syndromes,[28,86] and to atrophy and white matter connectivity of the pre-supplementary motor area—a cortical region that lies at the intermediate level of a spatially embedded cognitive hierarchy for behaviour, between motor cortex and prefrontal cortex.[28,40]

There are therapeutic implications of active inference. For example, akinesia can be improved by high frequency peripheral vibration which reduces the precision of sensory evidence and increasing the relative precision of sensorimotor predictions (*cf.* Sweeney *et al.*[29] and Macerollo *et al.*[30]). This is in line with suggestions that high-frequency vibration attenuates proprioceptive feedback allowing for greater top-down control.[87] A physiological correlate is the decrease of power of beta oscillations at the onset of the vibration, preceding the improved movement. Similar beta desynchronization[13,88,89] is essential for movement planning and initiation.[90] In bradykinetic disorders, beta power is elevated,[91–94] while dopaminergic treatment in Parkinson's disease enhances beta desynchronization,[93,95] alleviates akinesia, and increases sensorimotor attenuation.[28,96] Under active inference, beta power may index somatosensory precision and therefore mediate sensorimotor attenuation, modulated by dopamine.[28,96]

A lack of behaviour can also be caused by apathy, without akinesia. Apathy is common in dementia, including Alzheimer's disease, dementia with Lewy bodies, frontotemporal dementia and vascular dementia.[97–99] We propose that apathy arises from deficits in the precision of the higher order predictions of goal-states and context rather than proprioception (Fig. 1C). This is analogous to the causes of akinesia, but at a higher level of a cognitive hierarchy for goal-directed behaviour.[100] When the relative precision of the goal prior is low, it will fail to propagate through the hierarchy down to effector mechanisms, and the outcome is a lack of behaviour.[57,85,101] The failure of active inference thereby shifts from lack of movement (akinesia) to a lack of goal-directed behaviour (apathy) according to the level of the hierarchy in which precision is affected by the cellular and pharmacological effects of each molecular pathology.

In healthy controls, trait apathy is associated with lower precision of predictions about action outcomes.[100] In dementia-related apathy, there is limited direct evidence for higher variance of priors, but indirect support comes from the failure to modulate prefrontal cortical beta oscillations in goal-directed tasks and the correlation between challenging everyday behaviours and beta-power (specifically, the failure of task-related beta-desynchronization).[102] We suggest an anatomical correlate of goal priors lies in anterior cingulate and medial prefrontal cortex, with loss of connectivity to motor cortex and the striatum.[86,103–105]

Disinhibited and impulsive behaviours are common to many dementias,[98,106,107] with a predisposition to act out of context, prematurely, or on the basis of little evidence.[108] Such behaviours would be explained by impaired precision of high-order predictions which diminish the confidence weighting on the choices or behavioural policies available. This can lead to 'jumping to conclusions'.[109] Dopamine dysregulation may explain some types of impulsivity (e.g. Parkinson's disease[110]), but other neurotransmitters such as noradrenaline, GABA, and glutamate, modulate behavioural control and are also deficient in many neurodegenerative disorders.[2] For example, noradrenaline regulates impulsive behaviour via widespread projections from the locus coeruleus to the cortex,[111–113] in response to salient cues that trigger shifts in behaviour.[114] In the predictive coding framework, the locus coeruleus noradrenergic signals update predictions at higher levels mediated

by fronto-striatal circuits, in response to prediction error (e.g. 'surprise').[115] The locus coeruleus is affected by Alzheimer's disease, Parkinson's disease and frontotemporal lobar degeneration,[111] which has led to noradrenergic treatment strategies to reduce impulsivity.[116–118] In active inference terms, behaviours become impulsive and inflexible when the precision of priors is not updated in response to salient behavioural cues.

Memory and learning

Memory deficits and poor learning are prominent features of dementia, including but not limited to Alzheimer's disease. The degeneration of the medial temporal lobe may affect memory retrieval and associative learning in part because of the disruption of predictive coding in these circuits. The hippocampus encodes expectancies of future events based on the probabilistic consequences of past events,[119–121] and hippocampal activity is modulated by the predictability of the future events.[122] Hippocampus not only encodes individual episodes but also the ordinal structure of events, a distributed in space, time (time in relation to internal computational demands, not an external clock) or other properties. The representation of ordinal structure may appear as encoding sequences or locations, but it can also be seen as part of a more fundamental generative model of the environment—an 'inference machine' engaged in predictive coding.[123,124] Such a hippocampal-based hierarchy operates over multiple timescales.

The ability to anticipate events over very short timescales is impaired by many dementias. For example, oddball tasks such as the auditory mismatch negativity paradigm have been interpreted to rely on short term 'memory traces' for sensory events. Such tasks have provided some of the strongest direct evidence for predictive coding.[14,125–129] The mismatch response indexes the prediction error, that is fed-forward in a frontotemporal hierarchy to update predictions that are in turn fed backwards.[126] The active nature of auditory predictions has been corroborated by computational and dynamic causal modelling. Simulations show that the mismatch response is an output of active cortical predictions rather than passive synaptic habituation.[128] Omitted events in mismatch paradigms provide an ideal test of cortical hierarchies that actively predict events. Indeed, dynamic causal modelling of omitted events show increased connectivity from and to the prefrontal cortex similar to the connectivity changes observed for the mismatch stimuli.[130] In dementia, the mismatch negativity amplitude is reduced,[69,131,132] together with impaired frontotemporal connectivity (Fig. 2A).[22,69,133,134] Patients with Alzheimer's disease show larger reductions at longer inter-stimulus intervals[37,67,135] in relation to reduced temporal activity and cognitive score of executive function.[131,136]

Patients with Alzheimer's disease have difficulty encoding and processing novel information (e.g. high rates of false recognition of novel items,[137,138] reduced primacy,[139,140] von Restorff effect[141]) associated with reduced functional connectivity between hippocampus, temporal and frontal areas.[142] Asymptomatic *APOE4* carriers compared to non-carriers, show reduced prediction errors to novel words, and elevated hippocampal activity to subsequently remembered words.[143] In those at risk of familial Alzheimer's disease, *PSEN1* and *APP* mutation carriers who approach the familial age of diagnosis, show elevated blood oxygenation level-dependent response in the middle temporal gyri during novelty encoding.[144] These impairments in novelty processing are consistent with impaired predictive processing in a hippocampal hierarchy. Larger prediction errors generated after encountering novel or contextually unexpected items (e.g. 'the butcher in the *office*'), drive stronger episodic encoding compared to expected items (e.g. 'the butcher in the butcher *shop*').[145,146] Unsuccessful learning could therefore result from smaller prediction errors arising from relatively low precision weighting of the prediction error.[145,147]

At the cellular level, the modulation of the precision of a hippocampal prediction error in memory tasks is dependent on both cholinergic and dopaminergic modulation of NMDA receptor plasticity[14,148–151] Impaired mismatch response in Alzheimer's disease is partially explained by the degeneration of cholinergic projections, in the presence of relatively preserved top-down propagation of predictions from intact higher level priors.[136] Cholinergic agents partially restore the mismatch response in Alzheimer's disease,[42] enhancing feed-forward signalling by precision of the sensory evidence weighting.[14,152] Similarly, dopamine is proposed to modulate saliency of the stimuli in hippocampus in response to novelty and facilitate encoding of the new information via its connections with the ventral tegmental area and substantia nigra.[150,151,153–155] Supporting this, administration of dopamine agonists, accelerates the processing speed of novel information,[156] and enhances recollection.[157] GABAergic modulation of feedback predictions and feedforward prediction errors may also contribute to the impairment of predictive coding from frontotemporal lobar degeneration.[23,24]

Speech and language

In health, language comprehension shows remarkable speed and resistance to noisy environments. This is enabled by predictive coding at multiple levels of linguistic representation: phonological,[158–160] semantic,[161–166] syntactic[167–169] and discourse context.[170] In neurodegenerative aphasias, poor comprehension arises from the impact of lesions on the frontotemporal and temporo-parietal networks which support top-down propagation and updating of predictions. For example, people with non-fluent variant primary progressive aphasia show particular vulnerability to processing deficits and delays at the lexical level when speech inputs are degraded[171,172] or ambiguous.[173–175] This arises from degeneration of frontal and perisylvian cortex, with reduction of top-down control used to optimize perception and production of speech,[176–179] leading to speech production deficits and agrammatism,[180–182] In contrast, damage to the temporo-parietal junction leads to speech repetition deficits[183,184] arising from disrupted mapping between priors for speech representations and proprioceptive articulatory predictions in the ventral motor cortex and inferior frontal cortex.[84,185]

Cope *et al.*[186] showed that in the presence of intact temporal cortex, frontal lobe neurodegeneration from non-fluent variant primary progressive aphasia causes overly precise contextual priors, together with reduced frontal-to-temporal directional connectivity in the beta frequency range (Fig. 2B–D). This combination leads to delayed resolution of speech inputs by the temporal cortex, and impaired perception of degraded speech input. The reliance on overly precise priors explains the paradoxical relative advantage for patients as noise increases (in contrast to healthy adults). The patients' speech comprehension deficit was more severe in quiet settings. Overly precise priors may also affect speech production in primary progressive aphasia: whereas delayed auditory feedback in healthy controls reduces fluency and accuracy of speech,[187,188] delayed feedback does not impair fluency. This suggests a reliance on internal models of speech and relative weakness of the precision of sensory representations.[189]

Efficient reading requires top-down signalling from higher order language areas, to disambiguate visually confusable words.[190] While damage to the left medial occipito-temporal areas causes alexia and object agnosia with spared central language abilities and orthographic knowledge,[191,192] reading deficits are often

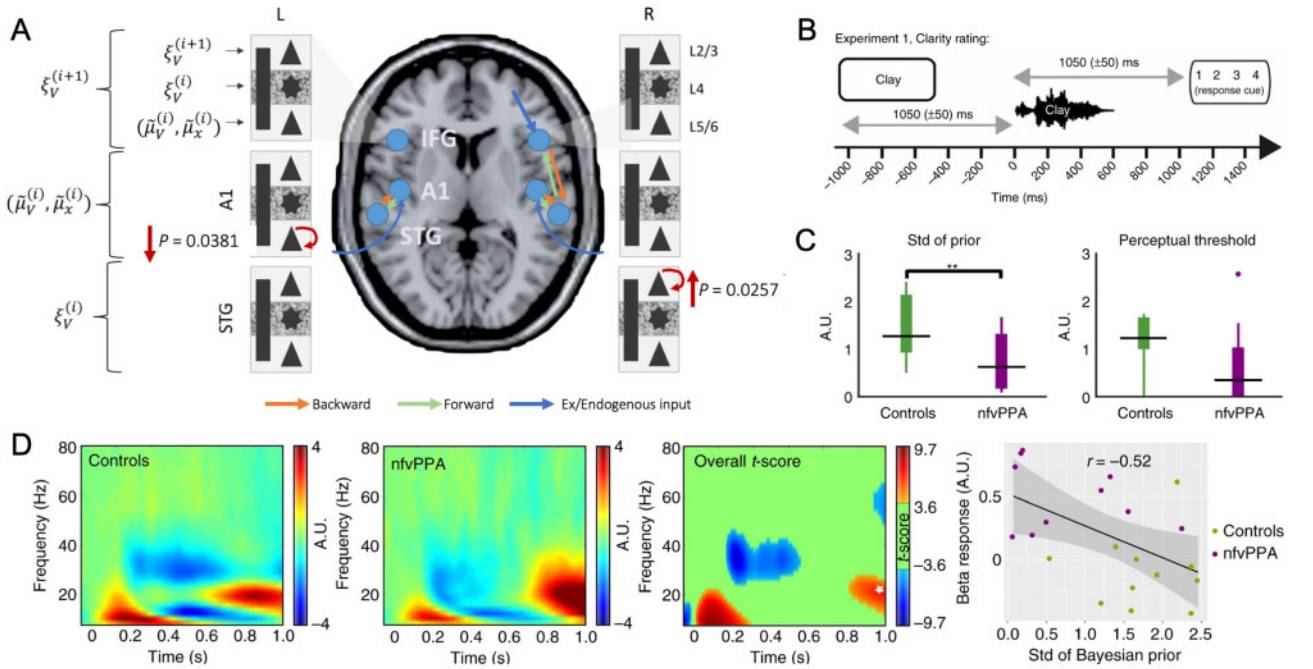

Figure 2 Neurophysiological changes associated with predictive coding impairments. (**A**) Cortical microcircuit dynamic causal model of the mismatch negativity response in patients with behavioural variant frontotemporal dementia, compared with healthy controls. Local (intrinsic) decreases in self-modulation of the deep pyramidal cells in the primary auditory cortex (A1), and increases in self-modulation of the superficial pyramidal cells in the superior temporal gyrus, lead to failure to establish sensory predictions and thereby reduced mismatch response. (**B**) Illustration of the MEG paradigm used by Cope *et al.*,[186] in which participants were presented with a written word followed by a noise vocoded spoken word that either matched or mismatched with the written word. Participants rated the clarity of the spoken words. (**C**) Derived parameters from Bayesian data modelling show that patients with non-fluent primary progressive aphasia (nvPPA) had more precise priors (smaller variance) than controls. A.U. = arbitrary units. (**D**) Induced responses between the cue offset and spoken word onset: beta power was higher in the nvPPA group after 800 ms and negatively correlated with precision of the prior expectations. **A** is reprinted from Shaw *et al.*[22] with permission. **B–D** are reprinted from Cope *et al.*[186] with permission.

more severe than object recognition deficits. Lesions of inferior frontal cortex cause auditory agnosias and pure word deafness.[193,194] Woodhead *et al.*[195] showed that whole-word training to improve reading was associated with stronger feedback connectivity from the inferior frontal gyrus to the occipital areas, and bidirectional connectivity between ventral occipito-temporal and occipital areas. This suggests stronger top-down priors aid prediction of the words in reading.

Semantic processing of words in context is similarly dependent on top-down signalling, as contextual information and prior knowledge is used to predict forthcoming words.[165,196,197] The N400 is an electrophysiological index of the prediction error, reflecting the degree of mismatch between semantic priors and sensory input.[198] In semantic dementia differentiation of concepts that belong to the same semantic category is impaired, such as 'giraffe' and 'zebra' (i.e. taxonomic blurring). The N400 is absent for mismatches of the same semantic category,[199] suggesting that semantic priors are under-specified (i.e. imprecise). Furthermore, disambiguating meaningful objects (but not meaningless shapes) in difficult viewing conditions is also impaired,[200] suggesting a domain-general deficit of top-down semantic control, thought to depend on intact connectivity within the larger fronto-temporo-parietal network.[201]

Conclusion

We propose a reformulation of cognitive deficits in dementia away from specific localized functional-anatomical impairments towards a generalized framework of aberrant Bayesian inference, within cortical hierarchies. Predictive coding principles can be generalized to account for multiple cognitive and perceptual impairments observed in neurodegenerative diseases, arising from diverse molecular aetiologies. The cognitive deficits and related neurophysiological abnormalities, can be understood in terms of altered precision in the normally finely-balanced feedforward and feedback pathways in cortical hierarchies. There are multiple potential cellular and molecular pathological routes to disrupt the precision of predictions and prediction errors, including localized cell loss (atrophy), and changes in acetylcholine, dopamine, and noradrenaline, that weight the importance (i.e. precision) of predictions and gain function of prediction errors. The predictive coding framework provides a unifying framework to understand the effects of these changes, in different hierarchical functional brain networks, as the basis for different dementia syndromes. It is a powerful trans-diagnostic framework that can aid better understanding of the mechanisms of disease across the lifespan and in turn facilitate new therapeutic strategies for dementia. New analytical methods enable new experimental medicine studies with techniques like dynamic causal modelling that can inform the efficacy and mechanism of candidate therapies. We therefore hope that this Update on predictive coding stimulates progress towards a new form of precision medicine, defined in terms of the precise cognitive and physiological consequences of disease.

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References

1. Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. Neurodegenerative diseases target large-scale human brain networks. *Neuron*. 2009;62(1):42–52.
2. Murley AG, Rowe JB. Neurotransmitter deficits from frontotemporal lobar degeneration. *Brain*. 2018;141(5):1263–1285.
3. Friston KJ. A theory of cortical responses. *Philos Trans R Soc Lond B Biol Sci*. 2005;360(1456):815–836.
4. Bar M. The proactive brain: Using analogies and associations to generate predictions. *Trends Cogn Sci*. 2007;11(7):280–289.
5. Clark A. Whatever next? Predictive brains, situated agents, and the future of cognitive science. *Behav Brain Sci*. 2013;36(3):181–204.
6. Rao RP, Ballard DH. Predictive coding in the visual cortex: A functional interpretation of some extra-classical receptive-field effects. *Nat Neurosci*. 1999;2(1):79–87.
7. Barlow HB. What is the computational goal of the neocortex? In: Koch C, Davis JL, eds. *Large-scale neuronal theories of the brain*. MIT Press; 1994:1–22.
8. Mumford D. On the computational architecture of the neocortex. II. The role of cortico-cortical loops. *Biol Cybern*. 1992;66(3):241–251.
9. Friston K, Kiebel S. Predictive coding under the free-energy principle. *Philos Trans R Soc Lond B Biol Sci*. 2009;364(1521):1211–1221.
10. Spratling MW. A review of predictive coding algorithms. *Brain Cogn*. 2017;112:92–97.
11. Aitchison L, Lengyel M. With or without you: Predictive coding and Bayesian inference in the brain. *Curr Opin Neurobiol*. 2017;46:219–227.
12. Brown H, Adams RA, Parees I, Edwards M, Friston K. Active inference, sensory attenuation and illusions. *Cogn Process*. 2013;14(4):411–427.
13. Palmer CE, Auksztulewicz R, Ondobaka S, Kilner JM. Sensorimotor beta power reflects the precision-weighting afforded to sensory prediction errors. *NeuroImage*. 2019;200:59–71.
14. Moran RJ, Campo P, Symmonds M, Stephan KE, Dolan RJ, Friston KJ. Free energy, precision and learning: The role of cholinergic neuromodulation. Randomized Controlled Trial Research Support, Non-U.S. Gov't. *J Neurosci*. 2013;33(19):8227–8236.
15. Collerton D, Perry E, McKeith I. Why people see things that are not there: A novel perception and attention deficit model for recurrent complex visual hallucinations. *Behav Brain Sci*. 2005;28(6):737–757; discussion 757–794.
16. O'Callaghan C, Kveraga K, Shine JM, Adams RB, Bar M. Predictions penetrate perception: Converging insights from brain, behaviour and disorder. *Conscious Cogn*. 2017;47:63–74.
17. Diederich NJ, Goetz CG, Stebbins GT. Repeated visual hallucinations in Parkinson's disease as disturbed external/internal perceptions: Focused review and a new integrative model. *Mov Disord*. 2005;20(2):130–140.
18. Yu AJ, Dayan P. Uncertainty, neuromodulation, and attention. *Neuron*. 2005;46(4):681–692.
19. Rosch RE, Auksztulewicz R, Leung PD, Friston KJ, Baldeweg T. Selective prefrontal disinhibition in a roving auditory oddball paradigm under N-methyl-D-aspartate receptor blockade. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2019;4(2):140–150.
20. Rosburg T, Kreitschmann-Andermahr I. The effects of ketamine on the mismatch negativity (MMN) in humans—a meta-analysis. *Clin Neurophysiol*. 2016;127(2):1387–1394.
21. Schmidt A, Diaconescu AO, Kometer M, Friston KJ, Stephan KE, Vollenweider FX. Modeling ketamine effects on synaptic plasticity during the mismatch negativity. *Cereb Cortex*. 2013;23(10):2394–2406.
22. Shaw AD, Hughes LE, Moran R, Coyle-Gilchrist I, Rittman T, Rowe JB. In vivo assay of cortical microcircuitry in frontotemporal dementia: A platform for experimental medicine studies. *Cereb Cortex*. 2021;31(3):1837–1847.
23. Adams NE, Hughes LE, Phillips HN, et al. GABA-ergic dynamics in human frontotemporal networks confirmed by pharmaco-magnetoencephalography. *J Neurosci*. 2020;40(8):1640–1649.
24. Adams N, Hughes L, Rouse M, et al. GABAergic cortical network physiology in frontotempoal lobar degeneration. *Brain*. 2021;144(7):2135–2145.
25. Xiang Z, Huguenard JR, Prince DA. Cholinergic switching within neocortical inhibitory networks. *Science*. 1998;281(5379):985–988.
26. Buia C, Tiesinga P. Attentional modulation of firing rate and synchrony in a model cortical network. *J Comput Neurosci*. 2006;20(3):247–264.
27. Baldeweg T, Wong D, Stephan KE. Nicotinic modulation of human auditory sensory memory: Evidence from mismatch negativity potentials. *Int J Psychophysiol*. 2006;59(1):49–58.
28. Wolpe N, Zhang J, Nombela C, et al.; Cam-CAN. Sensory attenuation in Parkinson's disease is related to disease severity and dopamine dose. *Sci Rep*. 2018;8(1):15643.
29. Sweeney D, Quinlan L, Browne P, Richardson M, Meskell P, ÓLaighin G. A technological review of wearable cueing devices addressing freezing of gait in Parkinson's disease. *Sensors (Basel)*. 2019;19(6):1277.
30. Macerollo A, Palmer C, Foltynie T, et al. High-frequency peripheral vibration decreases completion time on a number of motor tasks. *Eur J Neurosci*. 2018;48(2):1789–1802.
31. Wolpe N, Ingram JN, Tsvetanov KA, et al.; Cam-CAN. Ageing increases reliance on sensorimotor prediction through structural and functional differences in frontostriatal circuits. *Nat Commun*. 2016;7:13034.
32. Friston KJ. Hallucinations and perceptual inference. *Behav Brain Sci*. 2005;28(6):764–766.
33. Sterzer P, Adams RA, Fletcher P, et al. The predictive coding account of psychosis. *Biol Psychiatry*. 2018;84(9):634–643.
34. Corlett PR, Horga G, Fletcher PC, Alderson-Day B, Schmack K, Powers AR. Hallucinations and strong priors. *Trends Cogn Sci*. 2019;23(2):114–127.
35. O'Callaghan C, Hall JM, Tomassini A, et al. Visual hallucinations are characterized by impaired sensory evidence accumulation: Insights from hierarchical drift diffusion modeling in Parkinson's disease. *Biol Psychiatry Cogn Neurosci Neuroimaging*. 2017;2(8):680–688.
36. Zarkali A, Adams RA, Psarras S, Leyland LA, Rees G, Weil RS. Increased weighting on prior knowledge in Lewy body-associated visual hallucinations. *Brain Commun*. 2019;1(1):fcz007.
37. Pekkonen E, Hirvonen J, Jääskeläinen IP, Kaakkola S, Huttunen J. Auditory sensory memory and the cholinergic system:

Implications for Alzheimer's disease. *Neuroimage*. 2001;14(2): 376–382.
38. Pekkonen E. Mismatch negativity in aging and in Alzheimer's and Parkinson's diseases. *Audiol Neurootol*. 2000;5(3-4):216–224.
39. Ballard C, Piggott M, Johnson M, et al. Delusions associated with elevated muscarinic binding in dementia with Lewy bodies. *Ann Neurol*. 2000;48(6):868–876.
40. Halliday G. Clarifying Lewy-body parkinsonism with visual hallucinations. *Lancet Neurol*. 2005;4(10):588–589.
41. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. *Brain*. 2002;125(Pt 2):391–403.
42. Engeland C, Mahoney C, Mohr E, Ilivitsky V, Knott VJ. Acute nicotine effects on auditory sensory memory in tacrine-treated and nontreated patients with Alzheimer's disease: An event-related potential study. *Pharmacol Biochem Behav*. 2002; 72(1-2):457–464.
43. Mori S, Mori E, Iseki E, Kosaka K. Efficacy and safety of donepezil in patients with dementia with Lewy bodies: Preliminary findings from an open-label study. *Psychiatry Clin Neurosci*. 2006;60(2):190–195.
44. Corlett PR, Honey GD, Krystal JH, Fletcher PC. Glutamatergic model psychoses: Prediction error, learning, and inference. *Neuropsychopharmacology*. 2011;36(1):294–315.
45. Hosoya T, Baccus SA, Meister M. Dynamic predictive coding by the retina. *Nature*. 2005;436(7047):71–77.
46. Hohwy J, Roepstorff A, Friston K. Predictive coding explains binocular rivalry: An epistemological review. *Cognition*. 2008; 108(3):687–701.
47. Vuust P, Ostergaard L, Pallesen KJ, Bailey C, Roepstorff A. Predictive coding of music–brain responses to rhythmic incongruity. *Cortex*. 2009;45(1):80–92.
48. Vuust P, Witek MA. Rhythmic complexity and predictive coding: A novel approach to modeling rhythm and meter perception in music. *Front Psychol*. 2014;5:1111.
49. Wicha NY, Moreno EM, Kutas M. Anticipating words and their gender: An event-related brain potential study of semantic integration, gender expectancy, and gender agreement in Spanish sentence reading. *J Cogn Neurosci*. 2004;16(7):1272–1288.
50. Dikker S, Pylkkänen L. Predicting language: MEG evidence for lexical preactivation. *Brain Lang*. 2013;127(1):55–64.
51. Lewis AG, Bastiaansen M. A predictive coding framework for rapid neural dynamics during sentence-level language comprehension. *Cortex*. 2015;68:155–168.
52. Lewis AG, Wang L, Bastiaansen M. Fast oscillatory dynamics during language comprehension: Unification versus maintenance and prediction? *Brain Lang*. 2015;148:51–63.
53. Kumar S, Sedley W, Nourski KV, et al. Predictive coding and pitch processing in the auditory cortex. *J Cogn Neurosci*. 2011; 23(10):3084–3094.
54. O'Doherty JP, Buchanan TW, Seymour B, Dolan RJ. Predictive neural coding of reward preference involves dissociable responses in human ventral midbrain and ventral striatum. *Neuron*. 2006;49(1):157–166.
55. Ramnani N, Miall RC. A system in the human brain for predicting the actions of others. *Nat Neurosci*. 2004;7(1):85–90.
56. Kilner JM. More than one pathway to action understanding. *Trends Cogn Sci*. 2011;15(8):352–357.
57. Friston KJ, Stephan KE, Montague R, Dolan RJ. Computational psychiatry: The brain as a phantastic organ. *Lancet Psychiatry*. 2014;1(2):148–158.
58. Fletcher PC, Frith CD. Perceiving is believing: A Bayesian approach to explaining the positive symptoms of schizophrenia. *Nat Rev Neurosci*. 2009;10(1):48–58.
59. Pellicano E, Burr D. When the world becomes 'too real': A Bayesian explanation of autistic perception. *Trends Cogn Sci*. 2012;16(10):504–510.
60. Lawson RP, Rees G, Friston KJ. An aberrant precision account of autism. *Front Hum Neurosci*. 2014;8:302.
61. Wolpe N, Hezemans FH, Rowe JB. Alien limb syndrome: A Bayesian account of unwanted actions. *Cortex*. 2020;127: 29–41.
62. Bregman AS. *Auditory scene analysis: The perceptual organization of sound*. MIT Press; 1990.
63. Griffiths TD, Warren JD. The planum temporale as a computational hub. *Trends Neurosci*. 2002;25(7):348–353.
64. Summerfield C, de Lange FP. Expectation in perceptual decision making: Neural and computational mechanisms. *Nat Rev Neurosci*. 2014;15(11):745–756.
65. Golden HL, Nicholas JM, Yong KX, et al. Auditory spatial processing in Alzheimer's disease. *Brain*. 2015;138(Pt 1): 189–202.
66. Goll JC, Kim LG, Ridgway GR, et al. Impairments of auditory scene analysis in Alzheimer's disease. *Brain*. 2012;135(Pt 1): 190–200.
67. Gaeta H, Friedman D, Ritter W, Cheng J. Changes in sensitivity to stimulus deviance in Alzheimer's disease: An ERP perspective. *Neuroreport*. 1999;10(2):281–287.
68. Laptinskaya D, Thurm F, Küster OC, et al. Auditory memory decay as reflected by a new mismatch negativity score is associated with episodic memory in older adults at risk of dementia. *Front Aging Neurosci*. 2018;10:5.
69. Hughes LE, Rowe JB. The impact of neurodegeneration on network connectivity: A study of change detection in frontotemporal dementia. *J Cogn Neurosci*. 2013;25(5):802–813.
70. Golden HL, Clark CN, Nicholas JM, et al. Music perception in dementia. *J Alzheimers Dis*. 2017;55(3):933–949.
71. Zimmermann J, Alain C, Butler C. Impaired memory-guided attention in asymptomatic APOE4 carriers. *Sci Rep*. 2019;9(1): 8138.
72. Uchiyama M, Nishio Y, Yokoi K, et al. Pareidolias: Complex visual illusions in dementia with Lewy bodies. *Brain*. 2012;135(Pt 8):2458–2469.
73. Barnes J, David AS. Visual hallucinations in Parkinson's disease: A review and phenomenological survey. *J Neurol Neurosurg Psychiatry*. 2001;70(6):727–733.
74. Mosimann UP, Rowan EN, Partington CE, et al. Characteristics of visual hallucinations in Parkinson disease dementia and dementia with Lewy bodies. *Am J Geriatr Psychiatry*. 2006;14(2): 153–160.
75. Pezzoli S, Cagnin A, Bandmann O, Venneri A. Structural and functional neuroimaging of visual hallucinations in Lewy body disease: A systematic literature review. *Brain Sci*. 2017; 7(12):84.
76. Yao N, Pang S, Cheung C, et al. Resting activity in visual and corticostriatal pathways in Parkinson's disease with hallucinations. *Parkinsonism Relat Disord*. 2015;21(2):131–137.
77. Shine JM, Muller AJ, O'Callaghan C, Hornberger M, Halliday GM, Lewis SJ. Abnormal connectivity between the default mode and the visual system underlies the manifestation of visual hallucinations in Parkinson's disease: A task-based fMRI study. *NPJ Parkinsons Dis*. 2015;1:15003.
78. Heitz C, Noblet V, Cretin B, et al. Neural correlates of visual hallucinations in dementia with Lewy bodies. *Alzheimers Res Ther*. 2015;7(1):6.
79. Peraza LR, Kaiser M, Firbank M, et al. fMRI resting state networks and their association with cognitive fluctuations in dementia with Lewy bodies. *Neuroimage Clin*. 2014;4:558–565.

80. Sanchez-Castaneda C, Rene R, Ramirez-Ruiz B, et al. Frontal and associative visual areas related to visual hallucinations in dementia with Lewy bodies and Parkinson's disease with dementia. *Mov Disord*. 2010;25(5):615–622.
81. Perneczky R, Drzezga A, Boecker H, Förstl H, Kurz A, Häussermann P. Cerebral metabolic dysfunction in patients with dementia with Lewy bodies and visual hallucinations. *Dement Geriatr Cogn Disord*. 2008;25(6):531–538.
82. Ramírez-Ruiz B, Martí MJ, Tolosa E, et al. Cerebral atrophy in Parkinson's disease patients with visual hallucinations. *Eur J Neurol*. 2007;14(7):750–756.
83. Stebbins GT, Goetz CG, Carrillo MC, et al. Altered cortical visual processing in PD with hallucinations: An fMRI study. *Neurology*. 2004;63(8):1409–1416.
84. Adams RA, Shipp S, Friston KJ. Predictions not commands: Active inference in the motor system. *Brain Struct Funct*. 2013; 218(3):611–643.
85. Friston KJ, Daunizeau J, Kilner J, Kiebel SJ. Action and behavior: A free-energy formulation. *Biol Cybern*. 2010;102(3):227–260.
86. Wolpe N, Moore JW, Rae CL, et al. The medial frontal-prefrontal network for altered awareness and control of action in corticobasal syndrome. *Brain*. 2014;137(Pt 1):208–220.
87. Conrad MO, Scheidt RA, Schmit BD. Effects of wrist tendon vibration on targeted upper-arm movements in poststroke hemiparesis. *Neurorehabil Neural Repair*. 2011;25(1):61–70.
88. Palmer C, Zapparoli L, Kilner JM. A new framework to explain sensorimotor beta oscillations. *Trends Cogn Sci*. 2016;20(5): 321–323.
89. Tan H, Wade C, Brown P. Post-movement beta activity in sensorimotor cortex indexes confidence in the estimations from internal models. Research support, Non-U.S. Gov't. *J Neurosci*. 2016;36(5):1516–1528.
90. Pfurtscheller G, Lopes da Silva FH. Event-related EEG/MEG synchronization and desynchronization: Basic principles. *Clin Neurophysiol*. 1999;110(11):1842–1857.
91. Moisello C, Blanco D, Lin J, et al. Practice changes beta power at rest and its modulation during movement in healthy subjects but not in patients with Parkinson's disease. *Brain Behav*. 2015; 5(10):e00374.
92. Bizovicar N, Dreo J, Koritnik B, Zidar J. Decreased movement-related beta desynchronization and impaired post-movement beta rebound in amyotrophic lateral sclerosis. *Clin Neurophysiol*. 2014;125(8):1689–1699.
93. Levy R, Lozano AM, Lang AE, Dostrovsky JO. Event-related desynchronization of motor cortical oscillations in patients with multiple system atrophy. *Exp Brain Res*. 2010;206(1):1–13.
94. Schnitzler A, Gross J. Normal and pathological oscillatory communication in the brain. *Nat Rev Neurosci*. 2005;6(4):285–296.
95. Brown P, Marsden CD. Bradykinesia and impairment of EEG desynchronization in Parkinson's disease. *Mov Disord*. 1999; 14(3):423–429.
96. Macerollo A, Chen JC, Korlipara P, et al. Dopaminergic treatment modulates sensory attenuation at the onset of the movement in Parkinson's disease: A test of a new framework for bradykinesia. *Mov Disord*. 2016;31(1):143–146.
97. Chow TW, Binns MA, Cummings JL, et al. Apathy symptom profile and behavioral associations in frontotemporal dementia vs dementia of Alzheimer type. *Arch Neurol*. 2009;66(7): 888–893.
98. Lansdall CJ, Coyle-Gilchrist ITS, Jones PS, et al. Apathy and impulsivity in frontotemporal lobar degeneration syndromes. *Brain*. 2017;140(6):1792–1807.
99. Tay J, Morris RG, Tuladhar AM, Husain M, de Leeuw FE, Markus HS. Apathy, but not depression, predicts all-cause dementia in cerebral small vessel disease. *J Neurol Neurosurg Psychiatry*. 2020;91(9):953–959.
100. Hezemans FH, Wolpe N, Rowe JB. Apathy is associated with reduced precision of prior beliefs about action outcomes. *J Exp Psychol Gen*. 2020;149(9):1767–1777.
101. Parr T, Rikhye RV, Halassa MM, Friston KJ. Prefrontal computation as active inference. *Cereb Cortex*. 2019;30:682–695.
102. Hughes LE, Rittman T, Robbins TW, Rowe JB. Reorganization of cortical oscillatory dynamics underlying disinhibition in frontotemporal dementia. *Brain*. 2018;141(8):2486–2499.
103. Passamonti L, Lansdall CJ, Rowe JB. The neuroanatomical and neurochemical basis of apathy and impulsivity in frontotemporal lobar degeneration. *Curr Opin Behav Sci*. 2018;22:14–20.
104. Le Heron C, Apps MAJ, Husain M. The anatomy of apathy: A neurocognitive framework for amotivated behaviour. *Neuropsychologia*. 2018;118(Pt B):54–67.
105. Nobis L, Husain M. Apathy in Alzheimer's disease. *Curr Opin Behav Sci*. 2018;22:7–13.
106. Borges LG, Rademaker AW, Bigio EH, Mesulam MM, Weintraub S. Apathy and disinhibition related to neuropathology in amnestic versus behavioral dementias. *Am J Alzheimers Dis Other Demen*. 2019;34(5):337–343.
107. Nombela C, Rittman T, Robbins TW, Rowe JB. Multiple modes of impulsivity in Parkinson's disease. *PLoS One*. 2014;9(1): e85747.
108. Dalley JW, Robbins TW. Fractionating impulsivity: Neuropsychiatric implications. *Nat Rev Neurosci*. 2017;18(3): 158–171.
109. FitzGerald TH, Schwartenbeck P, Moutoussis M, Dolan RJ, Friston K. Active inference, evidence accumulation, and the urn task. *Neural Comput*. 2015;27(2):306–328.
110. Averbeck BB, Djamshidian A, O'Sullivan SS, Housden CR, Roiser JP, Lees AJ. Uncertainty about mapping future actions into rewards may underlie performance on multiple measures of impulsivity in behavioral addiction: Evidence from Parkinson's disease. *Behav Neurosci*. 2013;127(2):245–255.
111. Betts MJ, Kirilina E, Otaduy MCG, et al. Locus coeruleus imaging as a biomarker for noradrenergic dysfunction in neurodegenerative diseases. *Brain*. 2019;142(9):2558–2571.
112. Berridge CW, Waterhouse BD. The locus coeruleus-noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Res Brain Res Rev*. 2003;42(1): 33–84.
113. Holland N, Robbins T, Rowe J. The role of noradrenaline in cognition and cognitive disorders. *Brain*. 2021;144(8):2243–2256.
114. Dayan P, Yu AJ. Phasic norepinephrine: A neural interrupt signal for unexpected events. *Network*. 2006;17(4):335–350.
115. Sales AC, Friston KJ, Jones MW, Pickering AE, Moran RJ. Locus Coeruleus tracking of prediction errors optimises cognitive flexibility: An active inference model. *PLoS Comput Biol*. 2019; 15(1):e1006267.
116. Rahman S, Robbins TW, Hodges JR, et al. Methylphenidate ('Ritalin') can ameliorate abnormal risk-taking behavior in the frontal variant of frontotemporal dementia. *Neuropsychopharmacology*. 2006;31(3): 651–658.
117. Kehagia AA, Housden CR, Regenthal R, et al. Targeting impulsivity in Parkinson's disease using atomoxetine. Randomized Controlled Trial Research Support, Non-U.S. Gov't. *Brain*. 2014; 137(7):1986–1997.
118. Rae CL, Nombela C, Rodriguez PV, et al. Atomoxetine restores the response inhibition network in Parkinson's disease. *Brain*. 2016;139(Pt 8):2235–2248.
119. Harrison LM, Duggins A, Friston KJ. Encoding uncertainty in the hippocampus. *Neural Netw*. 2006;19(5):535–546.

120. Strange BA, Duggins A, Penny W, Dolan RJ, Friston KJ. Information theory, novelty and hippocampal responses: Unpredicted or unpredictable? *Neural Netw*. 2005;18(3): 225–230.
121. Eichenbaum H, Dudchenko P, Wood E, Shapiro M, Tanila H. The hippocampus, memory, and place cells: Is it spatial memory or a memory space? *Neuron*. 1999;23(2):209–226.
122. Weiler JA, Suchan B, Daum I. Foreseeing the future: Occurrence probability of imagined future events modulates hippocampal activation. *Hippocampus*. 2010;20(6):685–690.
123. Friston K, Buzsáki G. The functional anatomy of time: What and when in the brain. *Trends Cogn Sci*. 2016;20(7):500–511.
124. Buzsáki G, Llinás R. Space and time in the brain. *Science*. 2017; 358(6362):482–485.
125. Garrido MI, Friston KJ, Kiebel SJ, Stephan KE, Baldeweg T, Kilner JM. The functional anatomy of the MMN: A DCM study of the roving paradigm. *Neuroimage*. 2008;42(2):936–944.
126. Garrido MI, Kilner JM, Kiebel SJ, Friston KJ. Dynamic causal modeling of the response to frequency deviants. *J Neurophysiol*. 2009;101(5):2620–2631.
127. David O, Kiebel SJ, Harrison LM, Mattout J, Kilner JM, Friston KJ. Dynamic causal modeling of evoked responses in EEG and MEG. *Neuroimage*. 2006;30(4):1255–1272.
128. Wacongne C, Changeux JP, Dehaene S. A neuronal model of predictive coding accounting for the mismatch negativity. *J Neurosci*. 2012;32(11):3665–3678.
129. Phillips HN, Blenkmann A, Hughes LE, et al. Convergent evidence for hierarchical prediction networks from human electrocorticography and magnetoencephalography. *Cortex*. 2016; 82:192–205.
130. Chennu S, Noreika V, Gueorguiev D, Shtyrov Y, Bekinschtein TA, Henson R. Silent expectations: Dynamic causal modeling of cortical prediction and attention to sounds that weren't. *J Neurosci*. 2016;36(32):8305–8316.
131. Jiang S, Yan C, Qiao Z, et al. Mismatch negativity as a potential neurobiological marker of early-stage Alzheimer disease and vascular dementia. *Neurosci Lett*. 2017;647:26–31.
132. Brønnick KS, Nordby H, Larsen JP, Aarsland D. Disturbance of automatic auditory change detection in dementia associated with Parkinson's disease: A mismatch negativity study. *Neurobiol Aging*. 2010;31(1):104–113.
133. Stam CJ, Jones BF, Manshanden I, et al. Magnetoencephalographic evaluation of resting-state functional connectivity in Alzheimer's disease. *Neuroimage*. 2006;32(3):1335–1344.
134. Beste C, Mückschel M, Rosales R, et al. Striosomal dysfunction affects behavioral adaptation but not impulsivity-Evidence from X-linked dystonia-parkinsonism. *Mov Disord*. 2017;32(4): 576–584.
135. Pekkonen E, Jousmäki V, Könönen M, Reinikainen K, Partanen J. Auditory sensory memory impairment in Alzheimer's disease: An event-related potential study. *Neuroreport*. 1994;5(18): 2537–2540.
136. Ruzzoli M, Pirulli C, Mazza V, Miniussi C, Brignani D. The mismatch negativity as an index of cognitive decline for the early detection of Alzheimer's disease. *Sci Rep*. 2016;6:33167.
137. Budson AE, Michalska KJ, Sullivan AL, Rentz DM, Daffner KR, Schacter DL. False recognition in Alzheimer disease: Evidence from categorized pictures. *Cogn Behav Neurol*. 2003;16(1):16–27.
138. Belleville S, Ménard MC, Lepage E. Impact of novelty and type of material on recognition in healthy older adults and persons with mild cognitive impairment. *Neuropsychologia*. 2011;49(10): 2856–2865.
139. Howieson DB, Mattek N, Seeyle AM, et al. Serial position effects in mild cognitive impairment. *J Clin Exp Neuropsychol*. 2011;33(3):292–299.
140. Cunha C, Guerreiro M, de Mendonça A, Oliveira PE, Santana I. Serial position effects in Alzheimer's disease, mild cognitive impairment, and normal aging: Predictive value for conversion to dementia. *J Clin Exp Neuropsychol*. 2012;34(8):841–852.
141. Vitali P, Minati L, Chiarenza G, et al. The Von Restorff effect in ageing and Alzheimer's disease. *Neurol Sci*. 2006;27(3):166–172.
142. Brueggen K, Kasper E, Dyrba M, et al. The primacy effect in amnestic mild cognitive impairment: associations with hippocampal functional connectivity. *Front Aging Neurosci*. 2016;8: 244.
143. Evans S, Dowell NG, Tabet N, King SL, Hutton SB, Rusted JM. Disrupted neural activity patterns to novelty and effort in young adult. *Brain Behav*. 2017;7(2):e00612.
144. Braskie MN, Medina LD, Rodriguez-Agudelo Y, et al. Increased fMRI signal with age in familial Alzheimer's disease mutation carriers. *Neurobiol Aging*. 2012;33(2):424.e11–424.e21.
145. Henson RN, Gagnepain P. Predictive, interactive multiple memory systems. *Hippocampus*. 2010;20(11):1315–1326.
146. van Kesteren MT, Ruiter DJ, Fernández G, Henson RN. How schema and novelty augment memory formation. *Trends Neurosci*. 2012;35(4):211–219.
147. Clark A. A nice surprise? Predictive processing and the active pursuit of novelty. *Phenomenol Cogn Sci*. 2018;17(3):521–534.
148. Miasnikov AA, Chen JC, Weinberger NM. Specific auditory memory induced by nucleus basalis stimulation depends on intrinsic acetylcholine. *Neurobiol Learn Mem*. 2008;90(2):443–454.
149. Carbajal GV, Malmierca MS. The neuronal basis of predictive coding along the auditory pathway: From the subcortical roots to cortical deviance detection. *Trends Hear*. 2018;22: 2331216518784822.
150. Düzel E, Bunzeck N, Guitart-Masip M, Düzel S. NOvelty-related motivation of anticipation and exploration by dopamine (NOMAD): Implications for healthy aging. *Neurosci Biobehav Rev*. 2010;34(5):660–669.
151. Lisman JE, Grace AA. The hippocampal-VTA loop: Controlling the entry of information into long-term memory. *Neuron*. 2005; 46(5):703–713.
152. Yu AJ, Dayan P. Acetylcholine in cortical inference. *Neural Netw*. 2002;15(4-6):719–730.
153. Lisman J, Grace AA, Duzel E. A neoHebbian framework for episodic memory; role of dopamine-dependent late LTP. *Trends Neurosci*. 2011;34(10):536–547.
154. Bunzeck N, Guitart-Masip M, Dolan RJ, Duzel E. Pharmacological dissociation of novelty responses in the human brain. *Cereb Cortex*. 2014;24(5):1351–1360.
155. Schultz W, Dayan P, Montague PR. A neural substrate of prediction and reward. *Science*. 1997;275(5306):1593–1599.
156. Eckart C, Bunzeck N. Dopamine modulates processing speed in the human mesolimbic system. *Neuroimage*. 2013;66:293–300.
157. Chowdhury R, Guitart-Masip M, Bunzeck N, Dolan RJ, Düzel E. Dopamine modulates episodic memory persistence in old age. *J Neurosci*. 2012;32(41):14193–14204.
158. Ettinger A, Linzen T, Marantz A. The role of morphology in phoneme prediction: Evidence from MEG. *Brain Lang*. 2014;129: 14–23.
159. Monsalve IF, Bourguignon M, Molinaro N. Theta oscillations mediate pre-activation of highly expected word initial phonemes. *Sci Rep*. 2018;8(1):9503.
160. Gagnepain P, Henson RN, Davis MH. Temporal predictive codes for spoken words in auditory cortex. *Curr Biol*. 2012;22(7): 615–621.
161. DeLong KA, Urbach TP, Kutas M. Probabilistic word pre-activation during language comprehension inferred from electrical brain activity. *Nat Neurosci*. 2005;8(8):1117–1121.

162. Lau EF, Holcomb PJ, Kuperberg GR. Dissociating N400 effects of prediction from association in single-word contexts. *J Cogn Neurosci*. 2013;25(3):484–502.
163. Lau EF, Nguyen E. The role of temporal predictability in semantic expectation: An MEG investigation. *Cortex*. 2015;68:8–19.
164. Maess B, Mamashli F, Obleser J, Helle L, Friederici AD. Prediction signatures in the brain: Semantic pre-activation during language comprehension. *Front Hum Neurosci*. 2016;10:591.
165. Klimovich-Gray A, Tyler LK, Randall B, Kocagoncu E, Devereux B, Marslen-Wilson WD. Balancing prediction and sensory input in speech comprehension: the spatiotemporal dynamics of word recognition in context. *J Neurosci*. 2019;39(3):519–527.
166. Wang L, Kuperberg G, Jensen O. Specific lexico-semantic predictions are associated with unique spatial and temporal patterns of neural activity. *Elife*.12: 2018;7:e39061.
167. Fonteneau E. Structural syntactic prediction measured with ELAN: Evidence from ERPs. *Neurosci Lett*. 2013;534:211–216.
168. Wlotko EW, Federmeier KD. Time for prediction? The effect of presentation rate on predictive sentence comprehension during word-by-word reading. *Cortex*. 2015;68:20–32.
169. Henderson JM, Choi W, Lowder MW, Ferreira F. Language structure in the brain: A fixation-related fMRI study of syntactic surprisal in reading. *Neuroimage*. 2016;132:293–300.
170. Otten M, Van Berkum JJ. Discourse-based word anticipation during language processing: Prediction of priming? *Discourse Process*. 2008;45(6):464–496.
171. Utman JA, Blumstein SE, Sullivan K. Mapping from sound to meaning: Reduced lexical activation in Broca's aphasics. *Brain Lang*. 2001;79(3):444–472.
172. Moineau S, Dronkers NF, Bates E. Exploring the processing continuum of single-word comprehension in aphasia. *J Speech Lang Hear Res*. 2005;48(4):884–896.
173. Hagoort P. Impairments of lexical-semantic processing in aphasia: Evidence from the processing of lexical ambiguities. *Brain Lang*. 1993;45(2):189–232.
174. Swaab TY, Brown C, Hagoort P. Understanding ambiguous words in sentence contexts: Electrophysiological evidence for delayed contextual selection in Broca's aphasia. *Neuropsychologia*. 1998;36(8):737–761.
175. Grindrod CM, Baum SR. Hemispheric contributions to lexical ambiguity resolution in a discourse context: Evidence from individuals with unilateral left and right hemisphere lesions. *Brain Cogn*. 2005;57(1):70–83.
176. Pickering MJ, Garrod S. Do people use language production to make predictions during comprehension? *Trends Cogn Sci*. 2007;11(3):105–110.
177. Pickering MJ, Garrod S. How tightly are production and comprehension interwoven? *Front Psychol*. 2013;4:238.
178. Park H, Ince RA, Schyns PG, Thut G, Gross J. Frontal top-down signals increase coupling of auditory low-frequency oscillations to continuous speech in human listeners. *Curr Biol*. 2015;25(12):1649–1653.
179. Sohoglu E, Davis MH. Perceptual learning of degraded speech by minimizing prediction error. Research Support, Non-U.S. Gov't. *Proc Natl Acad Sci U S A*. 2016;113(12):E1747–E1756.
180. Gorno-Tempini ML, Dronkers NF, Rankin KP, et al. Cognition and anatomy in three variants of primary progressive aphasia. *Ann Neurol*. 2004;55(3):335–346.
181. Hayes RA, Dickey MW, Warren T. Looking for a location: dissociated effects of event-related plausibility and verb-argument information on predictive processing in aphasia. *Am J Speech Lang Pathol*. 2016;25(4S):S758–S775.
182. Henry ML, Wilson SM, Babiak MC, et al. Phonological processing in primary progressive aphasia. *J Cogn Neurosci*. 2016;28(2):210–222.
183. Baldo JV, Klostermann EC, Dronkers NF. It's either a cook or a baker: Patients with conduction aphasia get the gist but lose the trace. *Brain Lang*. 2008;105(2):134–140.
184. Buchsbaum BR, Baldo J, Okada K, et al. Conduction aphasia, sensory-motor integration, and phonological short-term memory—an aggregate analysis of lesion and fMRI data. *Brain Lang*. 2011;119(3):119–128.
185. Parr T, Rees G, Friston KJ. Computational neuropsychology and bayesian inference. *Front Hum Neurosci*. 2018;12:61.
186. Cope TE, Sohoglu E, Sedley W, et al. Evidence for causal top-down frontal contributions to predictive processes in speech perception. *Nat Commun*. 2017;8(1):2154.
187. Huang X, Chen X, Yan N, et al. The impact of Parkinson's disease on the cortical mechanisms that support auditory-motor integration for voice control. *Hum Brain Mapp*. 2016;37(12):4248–4261.
188. Lin IF, Mochida T, Asada K, Ayaya S, Kumagaya S, Kato M. Atypical delayed auditory feedback effect and Lombard effect on speech production in high-functioning adults with autism spectrum disorder. *Front Hum Neurosci*. 2015;9:510.
189. Hardy CJD, Bond RL, Jaisin K, et al. Sensitivity of speech output to delayed auditory feedback in primary progressive aphasias. *Front Neurol*. 2018;9:894.
190. Price CJ, Devlin JT. The interactive account of ventral occipitotemporal contributions to reading. *Trends Cogn Sci*. 2011;15(6):246–253.
191. Damasio AR, Damasio H. The anatomic basis of pure alexia. *Neurology*. 1983;33(12):1573–1583.
192. Binder JR, Mohr JP. The topography of callosal reading pathways. A case-control analysis. *Brain*. 1992;115 (6):1807–1826.
193. Confavreux C, Croisile B, Garassus P, Aimard G, Trillet M. Progressive amusia and aprosody. *Arch Neurol*. 1992;49(9):971–976.
194. Otsuki M, Soma Y, Sato M, Homma A, Tsuji S. Slowly progressive pure word deafness. *Eur Neurol*. 1998;39(3):135–140.
195. Woodhead ZV, Penny W, Barnes GR, et al. Reading therapy strengthens top-down connectivity in patients with pure alexia. *Brain*. 2013;136(Pt 8):2579–2591.
196. Kocagoncu E, Clarke A, Devereux BJ, Tyler LK. Decoding the cortical dynamics of sound-meaning mapping. *J Neurosci*. 2017;37(5):1312–1319.
197. Lyu B, Choi HS, Marslen-Wilson WD, Clarke A, Randall B, Tyler LK. Neural dynamics of semantic composition. *Proc Natl Acad Sci U S A*. 2019;116(42):21318–21327.
198. Kutas M, Federmeier KD. Thirty years and counting: Finding meaning in the N400 component of the event-related brain potential (ERP). *Annu Rev Psychol*. 2011;62:621–647.
199. Hurley RS, Paller KA, Rogalski EJ, Mesulam MM. Neural mechanisms of object naming and word comprehension in primary progressive aphasia. *J Neurosci*. 2012;32(14):4848–4855.
200. Cumming TB, Patterson K, Verfaellie M, Graham KS. One bird with two stones: Abnormal word length effects in pure alexia and semantic dementia. *Cogn Neuropsychol*. 2006;23(8):1130–1161.
201. Ralph MA, Jefferies E, Patterson K, Rogers TT. The neural and computational bases of semantic cognition. *Nat Rev Neurosci*. 2017;18(1):42–55.