and *in vitro* disease models, biomarkers are yielding important insights into the *in vivo* dynamics of Alzheimer's disease in humans, and are revolutionizing the design of clinical trials (Andrieu *et al.*, 2015). It is only a matter of time before these advances transform the therapeutic landscape, and offer hope to the tens of millions of people suffering from this devastating disease.

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Conflict of interest

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References

Andrieu S, Coley N, Lovestone S, Aisen PS, Vellas B. Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions. Lancet Neurol 2015; 14: 926–44.

Blennow K, Mattsson N, Scholl M, Hansson O, Zetterberg H. Amyloid biomarkers in Alzheimer's disease. Trends Pharmacol Sci 2015; 36: 297–309.

Cairns NJ, Ikonomovic MD, Benzinger T, Storandt M, Fagan AM, Shah A, et al. Absence of Pittsburgh Compound B detection of CerebralAmyloid Beta in a patient with clinical, cognitive, and cerebrospinal fluid markers of Alzheimer Disease. Arch Neurol 2009; 66: 1557–62.

Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, Blennow K, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. Lancet Neurol 2014; 13: 614–29.

Jagust W. Is amyloid-beta harmful to the brain? Insights from human imaging studies. Brain 2016; 139 (Pt 1): 23–30.

Joshi AD, Pontecorvo MJ, Clark CM, Carpenter AP, Jennings DL, Sadowsky CH, et al. Performance characteristics of amyloid PET with florbetapir F 18 in patients with alzheimer's disease and cognitively normal subjects. J Nucl Med 2012; 53: 378–84.

Mattsson N, Insel PS, Donohue M, Landau S, Jagust WJ, Shaw LM, et al. Independent information from cerebrospinal fluid amyloid-beta and florbetapir imaging in Alzheimer's disease. Brain 2015; 138 (Pt 3): 772–83.

Palmqvist S, Mattsson N, Hansson O. Cerebrospinal fluid analysis detects cerebral beta-amyloid accumulation ealier than amyloid PET. Brain 2016; 139: 1226–36.

Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging and the Alzheimer's Association workgroup. Alzheimers Dement 2011; 7: 280–92.

Villemagne VL, Burnham S, Bourgeat P, Brown B, Ellis KA, Salvado O, et al. Amyloid beta deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. Lancet Neurol 2013; 12: 357–67.

Time in the orbitofrontal cortex

This scientific commentary refers to 'The neural dynamics of reward value and risk coding in the human orbitofrontal cortex' by Li *et al.* (doi: 10.1093/brain/awv409).

The ability to dynamically process complex reward-related signals is integral to adaptive human behaviour. For example, the human brain must rapidly synthesize information about reward value, probability and associated risk in order to successfully make decisions leading to positive outcomes. Further, complex neural processes may rely on activity spanning multiple timescales (Kringelbach *et al.*, 2015), which is likely to be critically important for understanding the neural computations associated with reward signals. Reward-related computations are widely considered to involve the orbitofrontal cortex (OFC), a brain region comprising a heterogeneous set of interacting areas or subregions. While numerous studies have made progress in characterizing the diverse functions of the OFC, these studies have primarily used spatial evidence from neuroimaging and neuropsychology (Kringelbach, 2005), and thus are limited in their ability to describe the dynamic properties of reward signals in the OFC. As a result, the spatiotemporal dynamics of reward-related processing in the human brain have largely remained elusive.

In the current issue of *Brain*, Li *et al.* (2016) circumvent this methodological constraint by measuring activity in the OFC using intracranial EEG in six patients with drug-refractory partial epilepsy. This technique offers a unique opportunity to directly record local field potentials (LFPs) from implanted depth electrodes, thereby affording superior temporal and spatial resolution in comparison to most other human neuroimaging methods. Using a probabilistic reward-learning task, the authors observed time-dependent differences in OFC responses

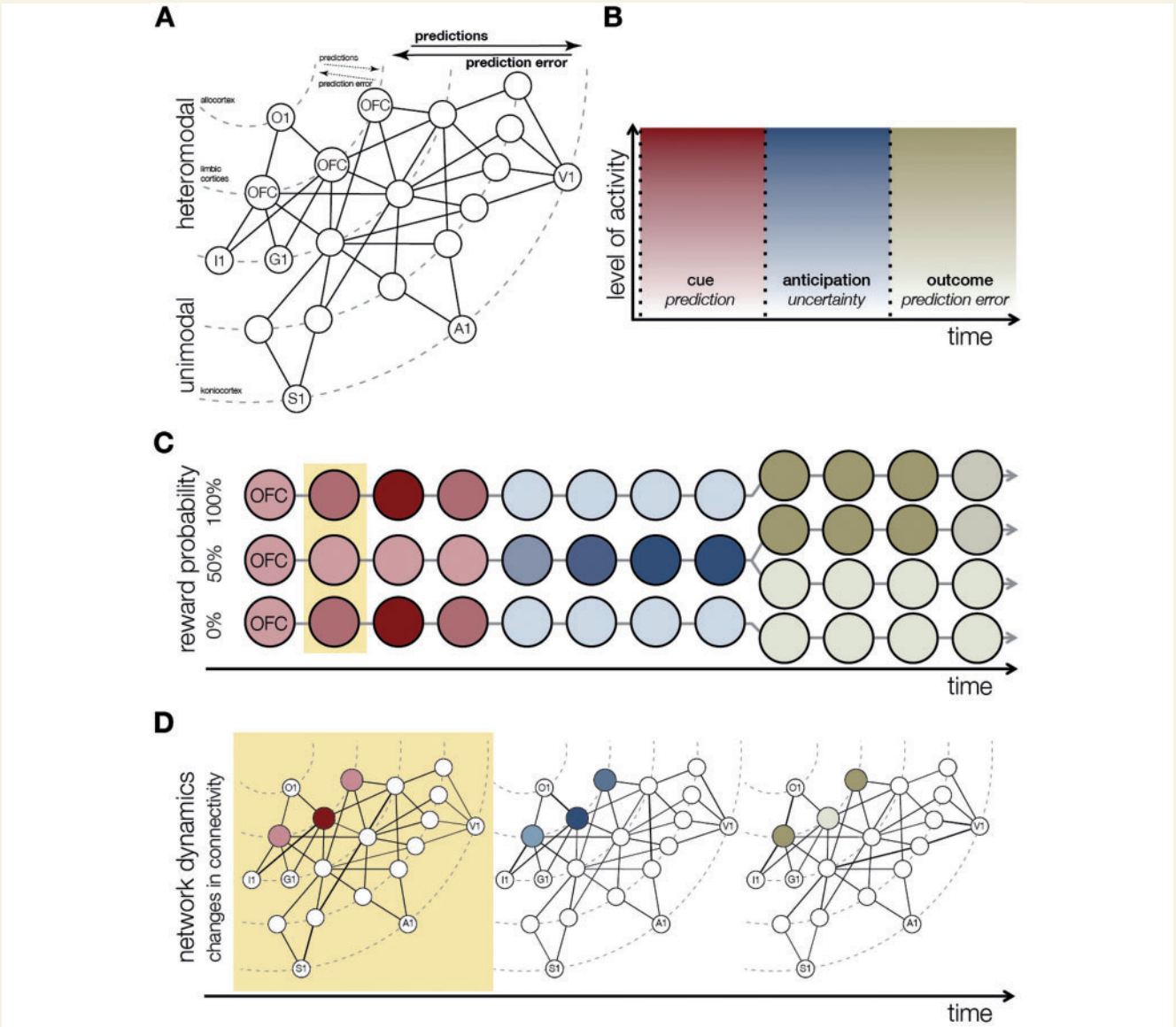

Figure 1 Reward-related signals in the OFC unfold dynamically across space and time. (**A**) Representative schematic of hierarchical cortical processing demonstrating higher-order limbic cortical regions (e.g. OFC) sending prediction signals to and receiving prediction error signals from multimodal, exteroceptive and interoceptive systems. A1 = primary auditory cortex; G1 = primary gustatory cortex; I1 = primary interoceptive cortex; O1 = primary olfactory cortex; S1 = primary somatosensory cortex; V1 = primary visual cortex. Each ring represents a different type of cortex, from less (interior circles) to greater (exterior circles) laminar differentiation. Figure is adapted from Mesulam (1998) and Chanes and Barrett (2016). (**B**) Conceptual representation of reward space for a task with distinct phases of cue (prediction, red), anticipation (uncertainty, blue) and outcome (prediction error, green) with darker colours signalling more reward-related activity. (**C**) Changes in level of activity in the OFC during phases of prediction, uncertainty, and prediction error based on neural evidence in Li *et al.* (2016). (**D**) Changes in network dynamics as a function of the activity in the OFC. Hypothetical illustration of the OFC directing functional network configurations as a key part of the global workspace across multiple brain regions over time.

associated with distinct reward signals (see Fig. 1). More specifically, they used a monetary reward task whereby participants were asked to learn associations between five reward probabilities (ranging from 0–100%) and various slot machines over the course of the experiment. Based on the reward probability of a given cue (i.e. the slot machine), participants could either receive 20€ (rewarded trials) or €0 (unrewarded trials) after a 1500 ms delay. Critically, this paradigm enabled the authors to distinguish between neural activity associated with reward probability, risk and experienced value signals.

Li *et al.* (2016) report three major findings related to the timing of reward signals in the OFC. First, they observed a positive association between LFP amplitudes and reward probability 400 ms after stimulus onset, suggesting that reward-related signals in the OFC arise shortly after a cue is presented and are more

Glossary

Beamformer: A spatially adaptive filter allowing for estimation of the amount of activity at any given location in the brain.

Primary and higher order rewards: Stimuli attaining positive motivational properties from brain processing. Primary rewards are closely related to individual/species survival (e.g. food and sex), while higher order rewards (e.g. money) are learned.

pronounced when the outcome is expected. Second, the OFC differentially responded to the five reward probabilities throughout late-stage anticipation and outcome phases, reaching a maximum less than 100 ms after outcome presentation. Interestingly, these responses did not distinguish between rewarded and unrewarded outcomes, but rather were maximally responsive at a 50% probability, implicating a risk signal related to uncertainty. Finally, the authors demonstrated an experienced value signal associated with the receipt of a reward (relative to no reward), with a functional bias for the lateral aspect of the OFC observed only in this phase.

The study conducted by Li and colleagues (2016) extends previous work on reward-related information processing by providing novel insights into the spatiotemporal properties underlying reward signals in the brain. By recording neural activity directly from intracranial electrodes during a monetary reward task, this study effectively demonstrates separable neural profiles arising from reward probability, risk and experienced value across time. Notably, this finding highlights the temporal heterogeneity—in addition to the well-established spatial heterogeneity—of the human OFC, thereby shedding light on the complexities of reward processing that rely not only on space but also on time. Finally, the study offers a unique perspective on our current understanding of reward dynamics and suggests several ways in which we can progress this understanding in future investigations.

One important limitation of the study by Li *et al.* (2016) is the use of intracranial recordings in participants with drug-refractory epilepsy. The considerations arising from this technique are 3-fold: first, findings in a population suffering from a neurological disease such as epilepsy may not be generalizable to the healthy human brain. Second, the intracranial EEG records from a limited set of electrodes, thereby constraining the spatial extent of sampling to a particular region or set of regions. Recent studies have argued in support of network-based approaches to understanding complex cognitive architectures (Petersen and Sporns, 2015), which capitalize on synchronous activity across large-scale collections of brain regions as opposed to activity within single regions. In this way, whole brain approaches may provide additional information important for reward-related processing that cannot readily be accessed through averaged activity within a single region of interest (e.g. the OFC). Finally, as the authors also point out, the OFC comprises a heterogeneous set of brain regions, and different types of rewards tend to engage different parts of the OFC. For example, a posterior to anterior gradient has been suggested to encode a spectrum of primary to higher order rewards, respectively (Kringelbach and Rolls, 2004; Sescousse *et al.*, 2010). However, implanted electrodes are likely to target subregions of the OFC inconsistent across participants, and may thus respond in variable ways to multiple reward domains. Taken together, characterization of the spatiotemporal dynamics of reward signals may benefit from network-based approaches to understanding how basic rewards (e.g. food, faces) as well as higher order rewards (e.g. money) are processed in the healthy brain.

As an alternative to invasive neuroimaging techniques, magnetoencephalography (MEG) studies have demonstrated promise for investigating time-dependent neural activity in the healthy human brain. Previous studies have observed rapid reward-related activity in the OFC (~130 ms) to salient visual stimuli requiring a fast orienting response, which is often followed by a second, slower wave of activity thought to reflect conscious cognitive processes (Bar *et al.*, 2006; Kringelbach *et al.*, 2008). Further, recent advances in MEG techniques have greatly improved the spatial localization of activity, for example, through the use of beamformers. Thus, MEG may be well suited to examining time-dependent reward dynamics across distributed brain areas in a healthy population.

However, standard approaches to non-invasive neuroimaging techniques primarily rely on correlational evidence. While causality can often be assessed directly in animal models (e.g. through pharmacological manipulations), recently developed computational models have begun to allow for assessment of probabilistic causality in humans. Building on theories of non-linear dynamical systems, whole-brain computational models have been used to efficiently characterize network-level communication across distributed sets of brain areas (i.e. functional connectivity) in order to investigate the spatiotemporal dynamics of brain organization and complex cognitive architectures (Deco *et al.*, 2015; Kringelbach *et al.*, 2015). Importantly, this dynamic characterization can incorporate time-dependent activity operating on varying timescales, which may capture a more complete picture of the spatiotemporal properties inherent to reward processing. Ultimately, efficient reward-related computations may require an optimal balance between fast and slow processes that additionally involve a distributed set of heterogeneous brain areas. Whole-brain models may provide a means to link studies aimed at understanding the temporal properties of reward (Li *et al.*, 2016) with the substantial progress that has been

made in understanding the spatial organization of reward signals. Future studies should aim to address the causal mechanisms underlying the large-scale neural dynamics of reward processes across space as well as time.

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References

Bar M, Kassam KS, Ghuman AS, Boshyan J, Schmid AM, Schmidt AM, et al. Top-down facilitation of visual recognition. Proc Natl Acad Sci USA 2006; 103: 449–54.

Chanes L, Barrett LF. Redefining the role of limbic areas in cortical processing. Trends Cogn Sci 2016; 20: 96–106. http://doi.org/10.1016/j.tics.2015.11.005

Deco G, Tononi G, Boly M, Kringelbach ML. Rethinking segregation and integration: contributions of whole-brain modelling. Nat Rev Neurosci 2015; 16: 430–9.

Kringelbach ML. The human orbitofrontal cortex: linking reward to hedonic experience. Nat Rev Neurosci 2005; 6: 691–702.

Kringelbach ML, Lehtonen A, Squire S, Harvey AG, Craske MG, Holliday IE, et al. A specific and rapid neural signature for parental instinct. PloS One 2008; 3: e1664.

Kringelbach ML, McIntosh AR, Ritter P, Jirsa VK, Deco G. The rediscovery of slowness: exploring the timing of cognition. Trends Cogn Sci 2015; 19: 616–28..

Kringelbach ML, Rolls ET. The functional neuroanatomy of the human orbitofrontal cortex: evid ence from neuroimaging and neuropsychology. Prog Neurobiol 2004; 72: 341–72.

Li Y, Vanni-Mercier G, Isnard J, Dreher JC. The neural dynamics of reward value and risk coding in the human orbitofrontal cortex. Brain 2016; 139: 1295–309.

Mesulam MM. From sensation to cognition. Brain 1998; 121: 1013–52.

Petersen SE, Sporns O. Brain networks and cognitive architectures. Neuron 2015; 88: 207–19.

Sescousse G, Redouté J, Dreher JC. The architecture of reward value coding in the human orbitofrontal cortex. J Neurosci 2010; 30: 13095–104.