syndrome. By contrast, performance on the Masked Prime Task differed between groups. Specifically, while the healthy control group showed clear evidence of negative-compatibility effects, this was not the case for the group with Tourette syndrome who exhibited a strong priming (facilitation) effect in response to presentation of the pre-cue. This was interpreted by the authors as evidence for an impairment in automatic inhibition mechanisms linked to action selection. They argue that we are continuously presented with environmental and internal cues that can trigger the initiation of movements, but these movements are typically suppressed by the operation of automatic inhibitory processes. In Tourette syndrome, these automatic inhibitory processes are impaired, giving rise to the expression of tics. They also argue that the automatic inhibitory processes are separate and independent from the inhibitory mechanisms linked to volitional control.

It should be noted that the view expressed by Rawji and colleagues is broadly consistent with the currently accepted view of Tourette syndrome pathophysiology, i.e. that the disorder is associated with impaired functioning of cortical-striatal-thalamic-cortical brain circuits and dysfunctional signalling of neurotransmitters such as dopamine and GABA. Specifically, it is thought that in Tourette syndrome, subsets of projection neurons become active in inappropriate contexts owing to impaired operation of inhibitory GABA interneurons within the striatum. This results in disinhibition of thalamo-cortical projections and hyper-excitability of limbic and motor regions, leading to the occurrence of tics. Support for this proposal comes from a very convincing 'striatal disinhibition' animal model of Tourette syndrome, which has shown that micro-injection of GABA antagonists within the striatum can produce tic-like movements in experimental animals (Bronfeld *et al.*, 2013; McCairn *et al.*, 2013). As Rawji *et al.* point out, the neural substrate underlying an impairment of automatic inhibition in Tourette syndrome is currently unknown, but is in our view likely to involve multiple levels within the cortical-striatal-thalamic-cortical brain circuits.

Georgina M. Jackson[1] *and Stephen R. Jackson*[2]

1 *Institute of Mental Health, School of Medicine, University of Nottingham, UK*

2 *School of Psychology, University of Nottingham, UK*

Correspondence to: Georgina M. Jackson
E-mail: georgina.jackson@nottingham.ac.uk

doi:10.1093/brain/awaa050

Competing interests

The authors report no competing interests.

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Virtual reality and real-time neurofeedback functional MRI: a breakthrough in foreseeing Alzheimer's disease?

This scientific commentary refers to 'Earliest amyloid and tau deposition modulate the influence of limbic networks during closed-loop hippocampal downregulation' by Skouras *et al.* (doi:10.1093/brain/awaa011).

Alzheimer's disease is the most common disease of ageing, and there are as yet no approved treatments that can revert or arrest its progression. According to the amyloid cascade hypothesis, the accumulation of amyloid-β peptides initiates the pathogenesis of Alzheimer's disease, leading to the formation of tau neurofibrillary tangles and to neurodegeneration that causes cognitive decline. Alzheimer's disease pathology can be detected *in vivo* by

quantifying amyloid-β protein and phosphorylated tau (p-Tau) in either CSF, or in the brain via PET. Alzheimer's disease is a continuum with pathological changes manifesting years before clinical symptoms. The preclinical phase of the disease is critical to identify early pathophysiological events and to develop interventions aimed at disease modification. Given that changes in synaptic function occur very early in the neurodegenerative process, functional MRI is particularly promising for detecting early alterations in brain function (Agosta *et al.*, 2017). Increased functional MRI activation in the hippocampus during episodic memory processing is recognized as a signature characteristic of the amnestic mild cognitive impairment stage of Alzheimer's disease (Dickerson *et al.*, 2005). Although elevated hippocampal activation was initially thought to be a compensatory mechanism, it has also been suggested that hippocampal hyperactivity may be detrimental and could be one factor driving amyloid-β deposition and neurodegeneration (Leal *et al.*, 2017). Indeed, functional MRI studies have shown that hippocampal hyperactivity occurs in cognitively unimpaired carriers of the apolipoprotein E (*APOE*) ε4 allele (Tran *et al.*, 2017) and in cognitively normal older adults with abundant brain amyloid-β deposits (Mormino *et al.*, 2012). Assessing functional reorganization associated with hippocampal hyperactivity in cognitively unimpaired adults at risk for Alzheimer's disease may thus shed light on the earliest functional changes resulting from Alzheimer's disease pathology. In this issue of *Brain*, Skouras and co-workers show that cognitively unimpaired adults at risk for Alzheimer's disease engage their brains differently compared to healthy elderly subjects when required to downregulate the hippocampus during a spatial navigation task (Skouras *et al.*, 2020). Those at risk of Alzheimer's disease show patterns of functional connectivity that resemble those observed during the resting state in patients with advanced Alzheimer's disease (Agosta *et al.*, 2017).

Skouras *et al.* used a powerful experimental approach that combined individual phenotyping, a virtual reality environment, real-time functional MRI neurofeedback, and network analysis (Fig. 1). They recruited 48 cognitively unimpaired adults at risk for Alzheimer's disease (i.e. descendants of patients and/or *APOE* ε4 carriers). The participants, who were part of the ongoing ALFA (Alzheimer's and Families) project (Molinuevo *et al.*, 2016), underwent deep clinical phenotyping, including demographic, lifestyle and cognitive characterization (Fig. 1A). Participants were classified as cognitively unimpaired based on their scores on the Clinical Dementia Rating Scale and the Mini-Mental State Examination. During the cognitive testing session, participants also completed the Free and Cued Selective Reminding Test, the Subjective Cognitive Decline Questionnaire, and the Visual Puzzles test included in the Wechsler Adult Intelligence Scale IV, which allowed for a sensitive and specific assessment of episodic memory, self-perceived cognitive decline, and visuospatial abilities, respectively. A blood sample for genetic analysis was obtained and the number of *APOE* ε4 alleles was determined for each participant. To evaluate the influence of Alzheimer's disease pathophysiological changes on functional connectivity patterns, Skouras *et al.* stratified individuals based on their levels of core Alzheimer's disease biomarkers in CSF. Eighteen participants had normal CSF biomarkers, 15 participants had low (abnormal) CSF amyloid-β_{42} levels, eight had high (abnormal) CSF p-Tau levels, and seven had both CSF abnormalities. In accordance with the NIA-AA Research Framework AT(N) biomarker classification scheme for Alzheimer's disease (Jack *et al.*, 2018), the latter seven participants can be classified as having preclinical Alzheimer's disease.

A major strength of the study by Skouras *et al.*, compared with previous functional MRI studies in Alzheimer's disease, is the use of a virtual reality environment and real-time functional MRI neurofeedback (Fig. 1B), which used principles of passive, sensory-aided, operant conditioning. Virtual reality enhances the ecological validity of task paradigms by providing realistic virtual environments in which participants can acquire new information and/or draw upon past memories to guide their behaviour. This approach is particularly useful in assessing neural correlates of memory, a complex function that relies on a range of interacting processes and systems (Reggente *et al.*, 2018). The use of virtual reality also promotes experimental compliance by making it easier for participants to complete long functional MRI tasks. Neurofeedback based on real-time functional MRI is a relatively novel neuroimaging application. The activity level of a single region of interest is provided as a feedback signal and participants are trained to up- or down-self-regulate the signal (Sitaram *et al.*, 2017). During a 30-min functional MRI session, participants in the study by Skouras *et al.* performed a spatial navigation task while encoding the features of the virtual reality environment, an activity that specifically engages the hippocampus. While immersed in the virtual reality environment, the participants' task was to use their hippocampal activity to control how fast they 'ran' along a fixed, circular path, while at the same time attending to features of the environment, remembering them and considering whether they changed from one lap to the next. In each real-time functional MRI neurofeedback session, images of whole-brain activity were acquired, reconstructed 'online' and exported every 3 s. Moment-to-moment changes in hippocampal CA1 activation triggered inverse changes in the velocity with which the participant was moving through the virtual environment. In brief, the first 30 functional volumes of the session were used to establish a baseline hippocampal CA1 activity (reference) for each participant. The most recent shift in hippocampal CA1 activity was compared to reference measures of change over the preceding 90 s. If the CA1 activity was below the reference, the velocity in the

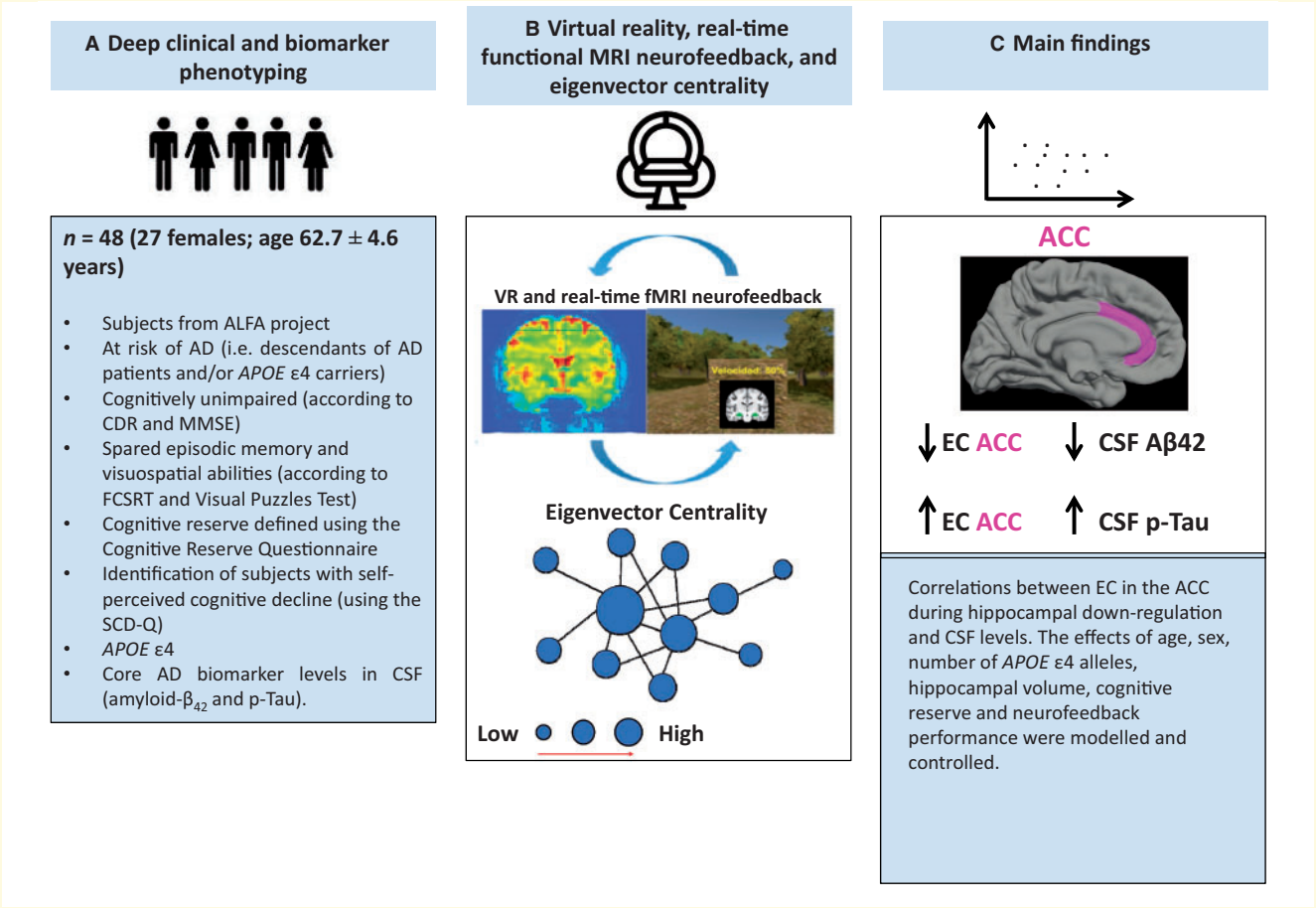

Figure 1 Study overview, strengths and main results from Skouras *et al.* (2020). (**A**) Cognitively unimpaired adults at risk for Alzheimer's disease underwent deep clinical and biomarker-based phenotyping. (**B**) The study used a powerful experimental approach involving a virtual reality (VR) environment, real-time functional MRI (fMRI) neurofeedback, and network science analysis. (**C**) Eigenvector centrality (EC) mapping was used to evaluate the functional connectivity of brain regions during a virtual reality spatial navigation task. The association between CSF amyloid-β_{42} and p-Tau levels and the eigenvector centrality of brain regions was assessed. In adults at risk for Alzheimer's disease, the eigenvector centrality of the anterior cingulate cortex (ACC) decreased with low CSF amyloid-β_{42} levels and increased with high CSF p-Tau levels. Aβ42 = amyloid-β_{42}; AD = Alzheimer's disease; ALFA = Alzheimer's and Families project; CDR = Clinical Dementia Rating Scale; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; p-Tau = phosphorylated tau; SCD-Q = Subjective Cognitive Decline-Questionnaire.

virtual reality environment increased by 5%; in the opposite case, it decreased by 5%. At any given moment, the current velocity was displayed as a percentage of the maximum velocity possible and a green or red (feedback) signal was superimposed on a coronal brain view, reflecting the direction of the most recent change. The participants were instructed to explore different cognitive strategies with the aim of achieving the maximum possible velocity and covering as much distance as possible.

Eigenvector centrality mapping (Lohmann *et al.*, 2010) was then used to test the patterns of brain network connectivity during the hippocampal CA1 downregulation task (Fig. 1B). In recent years, much of the brain connectivity field has turned to graph (or network) theory, an analytic language for describing complex networks (Bullmore and Sporns, 2009). Graph network analysis allows topological modelling and characterization, from local to global level, of the functional integrative bases that support brain behaviours. Eigenvector centrality is a graph theory index that measures the influence of a node (i.e. a brain region) in the network (Lohmann *et al.*, 2010). Eigenvector centrality defines the value of a node in the network according to the importance of its neighbours, i.e. a high eigenvector centrality means that a node is connected to many nodes which themselves have a large number of connections. Using this technique, Skouras *et al.* found that in cognitively unimpaired adults at risk of cognitive impairment due to Alzheimer's disease, low CSF amyloid-β_{42} levels were related to decreased eigenvector centrality in the anterior cingulate cortex (ACC) and primary motor cortex (Fig. 1C). With high CSF p-Tau levels, eigenvector centrality increased in the ACC, ventral striatum and left primary somatosensory cortex, whereas it

Glossary

Eigenvector centrality: Measures the influence of a node in a network. Relative scores are assigned to all nodes in a network based on the notion that connections to high scoring nodes contribute more to the score of the node in question than equal connections to low scoring nodes.

Neurofeedback: A training method whereby a person receives continuous real-time information about changes in neural activity in a particular brain region, which they use to learn to self-regulate and control the neural activity in that region to produce (conscious) changes in behaviour.

Real-time functional MRI: Enables the real-time (immediate) visualization of brain activations as they are being acquired.

Real-time functional MRI neurofeedback: A type of biofeedback in which real-time online functional MRI signals are used to guide self-regulation of brain function.

Virtual reality: A simulated environment, experienced through sensory stimuli, that can be similar to (or completely different from) the real world. Virtual reality environments can be used to present richly complex multimodal sensory information to a subject while they are immersed in the artificial world.

decreased in the main default mode network hubs such as the posterior cingulate cortex, precuneus and cuneus (Fig. 1C). The findings in the ACC are particularly interesting as the ACC is known to be involved in the cognitive, explicit processing of reward (Emmert *et al.*, 2016), such as that induced by a neurofeedback signal. With respect to Alzheimer's disease pathology, this study appears to suggest that eigenvector centrality in the ACC initially decreases but then subsequently increases again, contributing to altered hippocampal self-regulation and hyperactivity. Future studies should use a longitudinal framework to confirm such a dynamic trajectory in relation to the subsequent steps of the pathophysiological Alzheimer's disease cascade, and to better elucidate the contribution of other brain regions in controlling hippocampal self-regulation in the earliest phase of Alzheimer's disease. Future studies should also take advantage of the multitude of graph analysis metrics to understand the interactions between distinct neuronal units during the various cognitive and behavioural changes occurring in the early stages of the disease.

Skouras *et al.* attempted to control for confounding factors such as cognitive and brain reserve. Upon inclusion in the study, participants completed the Cognitive Reserve Questionnaire. In addition, the FreeSurfer pipeline was applied to T_1-weighted images to estimate each participant's normalized hippocampal brain volume, as a proxy of brain reserve. When analysing the eigenvector centrality data, Skouras *et al.* used these two measures to control for interindividual differences in the ability to cope with brain pathological changes (Stern, 2006).

In light of all of the above, the findings by Skouras *et al.* highlight the promise of graph analysis and connectome studies to map the effects of Alzheimer's disease pathological changes on brain networks, and to provide new insights into how neurodegeneration disseminates across the brain in the earliest (preclinical) phase of the disease.

Federica Agosta,[1,2] *Elisa Canu*[1] *and Massimo Filippi*[1,2,3]

1 *Neuroimaging Research Unit, Institute of Experimental Neurology, Division of Neuroscience, San Raffaele Scientific Institute, Milan, Italy*

2 *Vita-Salute San Raffaele University, Milan, Italy*

3 *Neurology Unit and Neurophysiology Unit, San Raffaele Scientific Institute, Milan, Italy*

Correspondence to: Dr Federica Agosta
E-mail: agosta.federica@hsr.it

doi:10.1093/brain/awaa038

Competing interests

F.A. is Section Editor of *NeuroImage: Clinical*; has received speaker honoraria from Biogen Idec, Novartis and Philips; and receives or has received research support from the Italian Ministry of Health, AriSLA (Fondazione Italiana di Ricerca per la SLA), and the European Research Council. E.C. has received research support from the Italian Ministry of Health. M.F. is Editor-in-Chief of the *Journal of Neurology*; received compensation for consulting services and/or speaking activities from Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries; and receives research support from Biogen Idec, Merck-Serono, Novartis, Teva Pharmaceutical Industries, Roche, Italian Ministry of Health, Fondazione Italiana Sclerosi Multipla, and ARiSLA (Fondazione Italiana di Ricerca per la SLA).

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