Queen Mary Innovation

Opportunity 2023104

Early detection of dementia using default mode network effective connectivity

A technology developed from functional MRI (fMRI) scans which uses dynamic modelling to map effective connectivity in the default-mode network (DMN). This can be used as a non-invasive population-based pre-diagnostic biomarker for predicting future dementia incidence.

Background

Dementia is a general term for the impaired ability to think or make decisions that interferes with doing everyday activities and Alzheimer's disease (AD) pathology being the most important contributor to dementia at the population level. Although there is currently no cure for dementia, an early diagnosis means its progress can be slowed down in some cases, so the person may be able to maintain their mental function for longer. Functional MRI (fMRI) measures endogenous fluctuations in blood oxygen-level-dependent (BOLD) signal across the brain, which in turn reflect regional neural activation, and when this scan is taken while the patient is not completing any cognitive activity is known as a resting-state fMRI (rs-fMRI). The ability to reliably detect early changes in neural function associated with AD would provide a platform for the development of individualized dementia-prevention strategies.

The Problem

The current problem with dementia diagnosis lies in its often late detection, which limits the efficacy of potential treatments and interventions that occur after the onset of clinical symptoms. There remains no effective diagnostic tool to provide an accurate diagnosis and prognosis of dementia. Early diagnosis and prognosis could enable timely therapeutic or other interventions, potentially slowing disease progression and preserving cognitive function, while also facilitating the development of more effective therapeutics and improving clinical trial design and recruitment.

Invention: Benefits & Application

QMUL researchers investigated whether effective connectivity changes in the default-mode network (DMN) can be used to make early predictions about dementia incidence and prognosis in a population cohort. The DMN is a brain network active during rest and involved in self-referential thoughts, and it is the core brains regions within the DMN that are most commonly implicated in altered functional connectivity and vulnerability to AD neurology, potentially contributing to memory deficits and cognitive decline. Spectral dynamic causal modelling was applied to rs-fMRI data in a nested case–control group from the UK Biobank. For each participant, BOLD time-series were extracted from ten pre-defined regions-of interest (ROIs), which together defined the DMN. The network included four mid-line ROIs: one ROI in each medial temporal lobe, and four lateral ROIs. A fully connected DCM was fitted to the cross-spectra of these time-series data (spectral DCM) to estimate the effective connectivity between each and every pair of ROIs in the ten-node network.

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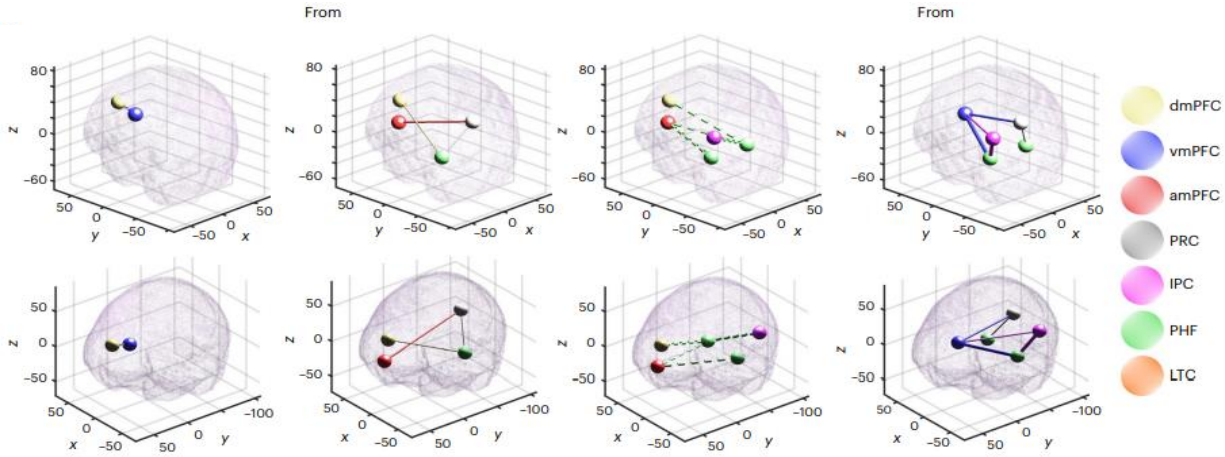

Figure 1: Effective connectivity differences between cases and controls visualized in Montreal Neurological Institute (MNI) space. Each tube represents a connection change. Solid tubes represent connections that are strengthened in cases compared with the controls; dashed tubes represent connections that are attenuated in cases compared with the controls; the thickness of the tube represents the magnitude of the connection change; and the colour of the tube represents the brain region from where the connection originates. The top row and bottom rows show the same data but from two different angles. The four columns display the following, respectively: attenuated excitatory connections, strengthened excitatory connections, attenuated inhibitory connections, strengthened inhibitory connections.

The development of this neurobiologically informed model of DMN effective connectivity was shown to enable accurate predictions about whether and when an individual will develop dementia. Dysconnectivity predicted both future dementia incidence (AUC = 0.82) and time to diagnosis (R = 0.53). It was also shown that the connectivity changes in the DMN are strongly associated with AD polygenic risk and social isolation, a risk factor that might accelerate the effects of pathological protein in the DMN.

The performance of the effective connectivity-based classifier exceeded that of classifiers based on volumetric and functional connectivity data, including structural MRI data as a unimodal predictor of future conversion to dementia. From a clinical perspective, this suggests that rs-fMRI could become a tool for identifying a neural network signature of dementia risk early in the pathological course of the disease. This type of non-invasive early detection of dementia is an increasingly valuable goal, particularly with the arrival of disease-modifying drugs. Early detection of dementia risk is also important in the context of targeted risk reduction strategies irrespective of underlying pathology.

Whereas pathology-specific biomarkers can guide disease-modifying molecular therapies, nonspecific biomarkers for all-cause dementia, such as those developed in this work, will be useful for identifying who is most likely to benefit from lifestyle changes and public health interventions, and when these interventions are likely to have the biggest impact. It is anticipated that, when combined with other data modalities such as amyloid beta and tau markers, effective connectivity would be likely to yield improved predictive performance.

Project Development

The team have developed a prototype which can accurately predict the likelihood of dementia before the clinical symptoms from rs-fMRI scans.

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Publication

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