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Advances in Neuroimaging to Support Translational Medicine in Dementia

A commissioned review for JNNP

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Abstract

Advances in neuroimaging are ideally placed to facilitate the translation from progress made in cellular genetics and molecular biology of neurodegeneration into improved diagnosis, prevention and treatment of dementia. New PET ligands allows one to quantify neuropathology, inflammation and metabolism *in vivo* safely and reliably, to examine mechanisms of human disease and support clinical trials. Developments in MRI based imaging and neurophysiology provide complementary quantitative assays of brain function and connectivity, for the direct testing of hypotheses of human pathophysiology. Advances in MRI are also improving the quantitative imaging of vascular risk and co-morbidities. In combination with large datasets, open data and artificial intelligence analysis methods, new informatics-based approaches are set to enable accurate single-subject inferences for diagnosis, prediction and treatment that have the potential to deliver precision medicine for dementia.

Here we show, through the use of critically appraised worked examples, how neuroimaging can bridge the gaps between molecular biology, neural circuits, and the dynamics of the core systems that underpin complex behaviours. We look beyond traditional structural imaging used routinely in clinical care, to include ultra-high field MRI (7T MRI), magnetoencephalography (MEG), and positron emission tomography (PET) with novel ligands. We illustrate their potential as safe, robust and sufficiently scalable to be viable for experimental medicine studies and clinical trials. They are especially informative when combined in multi-modal studies, with model-based analyses to test precisely defined hypotheses.

Highlights

- Neuroimaging can be used to establish and test models of disease mechanisms in humans.
- Positron emission tomography can quantify and localise molecular processes *in vivo*. Amyloid imaging has already changed clinical trials design and identified new drug targets.
- New ligands for synaptic density, protein synthesis, tau and other proteins are scientifically informative but have yet to find their place in healthcare.
- Neuronal populations are functionally and structurally connected at multiple scales, which can be examined by multimodal brain imaging.
- Relating molecular pathology to brain connectivity reveals disease mechanisms and validates drug targets.
- Focal neurodegenerative syndromes are important disease models, selectively perturbing complex neuronal systems.
- Powerful model-based analyses can reveal microcircuit-level consequences of neurodegeneration, in humans.
- Neuroimaging can enrich and stratify cohorts, for precision medicine approaches.
- Small-N experimental medicine studies and large-N observational trials enable the generation and testing of complementary hypotheses.
- Data sharing is now readily available, facilitated by consensus data formats and infrastructure like the Dementias Partnership UK Portal, enhancing the value of imaging data through Open Data initiatives, meta-analysis and repurposing. Disease-specific examples such as ADNI and PPMI, as well as global initiatives such as ENIGMA have transformed the field of collaborative research.
- Clinical trials can build on the success of longitudinal cohort studies combining behavioural and cognitive assessment with multi-modal imaging, genetics, serum and CSF measures.

Introduction

Brain imaging can bridge the gap between the progress made in understanding the cellular genetics and molecular biology of neurodegeneration [1-4] and clinical trials of novel interventions for dementia. The success of such translational medicine will be measured in terms of better diagnosis, treatment, and ultimately prevention (figure 1).

For diagnosis, improving current clinical practice requires quantitative methods that are not only accurate in terms of individual disease processes, but also allow precision medicine by accommodating the complex multidimensionality of dementia. The multidimensionality of disease has been recognised in psychiatry in the Research Domain Criteria [5], which provides a conceptual framework to integrate pathophysiology and symptomatology in disease spectra rather than arbitrary categories. The spectral, rather than discrete, nature of dementia phenotypes is increasingly recognised in trans-diagnostic cohort studies [6-8] and recent revisions of the diagnostic criteria and disease frameworks to encompass phenotypic variants [9-15].

For treatment trials, there are two complementary roles of imaging. The first role is to identify individuals who are well but who are at-risk for dementia at a later date, whether for genetic or unknown reasons, to track their latent or premanifest pathogenic mechanisms and potential therapeutic modifications [16-21]. The second role is in support of experimental medicine studies, in advance of late phase clinical trials, using surrogate markers of disease processes as treatment outcome. These secondary outcomes include measures of drug target engagement, and diverse measures of pathological protein burden, neurophysiological activity, brain connectivity, and function.

For prevention, imaging allows insight into potentially modifiable disease processes in terms of neurochemistry, physiology, molecular pathology and structure, and how these interact with the environment and the patient's underlying genetics. While no single imaging modality can quantify the cascade of events from root cause to final phenotype (figure 2), combinations of imaging methods can connect each of these causal processes [22 23].

The role of imaging to inform causal models of disease allows the design of rational, precise and optimally powered clinical trials. This is not a substitute for efficacy outcomes in trials, but a process of de-risking clinical trials, with better designs and endpoints that would support early closure of futile lines of enquiry so as to direct precious resources towards more promising goals.

Each of these applications of advanced imaging benefits from active engagement with the tools, and culture, for data sharing and integration – within and between modalities. We are entering a new age of large-scale collaborative efforts, which have proven so powerful in fields such as cancer biology.

This review aims to illustrate how advances in neuroimaging allow us to do much more than the structural imaging used clinically for differential diagnosis [24-27] and staging of disease [28-35]. Novel ligands for positron emission tomography can localise and relate molecular processes to each other *in vivo*. Combining these tools with the network-level connectivity analyses now possible on neurophysiological, functional and tract-based datasets allows the direct evaluation of hypotheses of disease progression. The use of focal neurodegenerative syndromes as disease models allows the delineation of core neuronal systems, which can then be related back to help us understand the complex behavioural abnormalities that arise in dementia. Model-based analyses can now reveal microcircuit-level consequences of neurodegeneration, generating hypotheses that can be directly evaluated in small-N experimental medicine studies, which are much more intensive and mechanisms-based than efficacy-oriented large-scale trials. As we move to human use of many emerging therapeutic candidates, the role neuroimaging in the trials is of particular importance, with

rich and transferrable datasets supporting mechanistic insights and Go/Nogo decisions for clinical trials.

Quantification of molecular

Current ligands for positron emission tomography (PET) allow the topographical quantification of metabolic activity (FDG), beta amyloid (e.g. PiB), tau neuropathology (e.g. flortaucepir), neuroinflammation (e.g. TSPO and P2X7R ligands), and synaptic loss (e.g. UCB-J).

In clinical practice, a commonly used ligand is [^{18}F]-fluorodeoxyglucose (FDG), to estimate regional metabolic activity, with longstanding evidence of partial utility for differentiating the major dementia syndromes [36 37]. FDG-PET has largely superseded single photon emission computed tomography (SPECT) quantification of regional blood flow, due to its greater resolution, signal to noise ratio, and robustness to non-linear relationships between metabolic demand and blood flow in cerebrovascular disease [38-40]. Clinically, it has value in delineating areas of hypometabolism to support diagnosis, but it can also be a trial outcome measure: tracking cerebral metabolic rate, a correlate of clinical measures with more statistical power [41].

The advent of Pittsburgh compound B (PiB), florbetapir, florbetben and flutemetamol have allowed the use of PET to quantify brain beta-amyloid [42]. Together with measurement of cerebro-spinal fluid amyloid and tau from lumbar puncture, amyloid-PET is applied in clinical practice. It is most commonly used to segregate mild cognitive impairment with underlying Alzheimer's pathology from other causes [43 44]. It can enrich study populations in clinical trials of early stage Alzheimer's disease, screening out the ~40% of patients with amnestic mild cognitive impairment who are amyloid negative [45 46]. It has proven sufficiently reliable to act as an *ante mortem* benchmark for validation of CSF biomarkers of Alzheimer's disease [47], as well as putative blood markers such as plasma phosphorylated tau 181 and 217 [48 49]. However, amyloid burden appears to stabilise by the time of diagnosis, and therefore these ligands have little utility in tracking Alzheimer's disease progression [50-53].

Longitudinal tracking of disease falls most promisingly to ligands binding hyperphosphorylated Tau, which have become available in the last decade. Tau-aggregates are a defining feature of AD and FTLD-tau, and are modifiers of PD and DLB. In AD, tau but not beta-amyloid distribution determines phenotype and severity [54]. In molecular terms it is hypothesised that a role of beta-amyloid in Alzheimer's disease is to promote the development and propagation of paired helical filaments of tau, which are neurotoxic in either their oligomeric or aggregated form [55-57]. This toxicity is amplified by the presence of beta-amyloid [58]. Several radioligands have been developed to assess regional Tau burden, including PBB3 [59] and THK5105 [60], but the most extensively evaluated is AV-1451, also known as T807 or flortaucepir [61 62]. This ligand has desirable properties *in vitro*, co-localising in post mortem samples with tau but not beta-amyloid, TDP-43 or synuclein [63]. It recapitulates the Braak stages of Alzheimer's disease progression [64-66], shows the expected patterns of regional distribution in focal subtypes [67], and is more closely linked to hypometabolism, atrophy and cognitive impairment than amyloid-PET [54].

Outside of Alzheimer's disease, Tau pathology characterises Progressive Supranuclear Palsy (PSP) [68], corticobasal degeneration (CBD) [69], and some forms of fronto-temporal dementia (FTD) [70 71], and is a modifier of outcomes in Lewy body disease [72]. However, in these non-AD diseases, the Tau isoforms differ, lacking the characteristic ultrastructure of paired helical filaments in Alzheimer's disease [73-75]. Despite relative *in vitro* insensitivity to these alternate isoforms, AV-1451 can identify the distribution of disease in PSP [76], CBS [77], and FTD due to some mutations of the Tau (MAPT) gene [78 79]. Binding affinity is lower than that seen in Alzheimer's disease, seemingly as a function of the

structural conformation of pathological Tau [80], and is very low in some Tau-mediated conditions such as non-fluent variant Primary Progressive Aphasia [22 81 82].

AV-1451 also shows non-specific binding properties, such that it can recapitulate the distribution of pathology in some diseases not mediated by Tau. For example, semantic dementia (also known as semantic variant Primary Progressive Aphasia), is characterised by abnormal aggregation of TDP-43 type C, in the absence of Tau [83 84]. AV-1451 binding is increased in those brain areas most affected by this TDP-mediated neurodegeneration [85 86] (without binding to TDP-43 itself). This lack of disease specificity is a barrier to some of the proposed roles of AV-1451, such as stratifying cases of FTD by underlying molecular sub-type, to enrich clinical trial cohorts. However, there remains the possibility of quantifying disease burden longitudinally across a range of disease [87], with differences in ligand binding affinity between disease sub-types controlled for by paired assessments within individuals. Second generation Tau ligands hold the promise of increasing specificity for Alzheimer-type Tau in paired helical filaments, but there remains an unmet need for specific PET ligands for FTLD-Tau, TDP-43 and synuclein.

Neuroinflammation is a common process across neurodegenerative diseases, demonstrating genetic [88-90] and epidemiological [91 92] association; and post-mortem [22 93 94] and CSF [95 96] concomitance; with possible mechanisms proposed in animal models [97-99]. This has led to the development of an array of PET radiotracers, targeting various stages of the neuroinflammatory cascade [100]. The most established target is the 18 kDa translocator protein (TSPO), which is upregulated in activated microglia (and to some extent astrocytes). In isolation, increases in microglial activation can be visualised *in vivo* across a range of neurodegenerative diseases [101-106], and the neuroinflammatory burden is correlated with cognitive performance [107-109]. Neuroinflammation seems to be an early process in disease pathogenesis, preceding clinical symptom onset in genetic cases [110], and demonstrating consistent involvement through the disease course [22 102-104]. Second generation TSPO ligands may have improved signal-to-noise, but inter-individual comparisons are confounded by genetic polymorphism [111]. Novel inflammation-related targets include the P2X7 receptor [112], which is expressed by microglia, and has been proposed as a therapeutic target in early Alzheimer's disease [113].

PET ligand development continues apace. Changes in synaptic density may precede atrophy and symptom onset [114-116], and this can be quantified by targeting synaptic vesicle glycoprotein 2A, SV2A with ligands such as ^{11}C-UCB-J, ^{11}C-UCB-J PET has revealed 20-40% reductions in regional synaptic density in AD and non-AD dementias, and in proportion to disease severity [116]. Cerebral protein synthesis rates can be measured with 11 L-[1-^{11}C] Leucine PET [117 118], a technique that has already been applied to children with developmental delay [119] and young adults with Fragile X syndrome [120], and holds particular promise for upcoming trials targeting the unfolded protein response [121].

Post synaptic pathology can also be measured by PET. For example, TARP γ8 regulates surface expression of post synaptic AMPA receptors [122], and ligands targeting this process are in human use, including early trials [121 123].

Advances in PET come partly in the form of new ligands, of different targets or greater sensitivity and specificity. However, there are also new ways to interrogate the PET data. For example, traditional analyses use mass-univariate "voxelwise" tests, or comparisons within specified regions-of-interest. In contrast, one can study the *distribution* of binding across disease sub-types. This is particularly powerful where the ligand has different affinity for individuals' molecular pathology, such as in AV-1451 ligand's affinity to protein pathology following different mutations of the Tau gene in frontotemporal dementia [78 110], or neuropathological subtypes of FTD [22 76 85 124]. Differences in affinity undermine the quantitative contrast between groups for any given region or voxel, but they do not prevent the multivariate approach assessing the similarity of ligand distributions, and classifying individuals into groups based on measures of clustering. This is analogous to the multi-

voxel pattern analysis techniques used for cognitive decoding in fMRI [125] and magnetoencephalography [126].

Molecular imaging is no longer solely the preserve of PET. Higher MRI field strengths open up the possibility of richer applications of spectroscopy, with signal to noise ratios sufficient for measurement of GABA possible *in vivo* in patients [127]. Quantitative Susceptibility Mapping (QSM) [128] can assess the regional burden paramagnetic substances, with iron particularly linked to cognition in both Alzheimer's [129] and Parkinson's [130] disease.

Neurodegenerative diseases are often accompanied by vascular comorbidity, with which they can interact bidirectionally [131]. For instance, enlarged perivascular spaces are pathways of clear interstitial fluid that may indicate a failure to clear fluid and waste products [132], including amyloid and tau protein [133-135]. Imaging the size and distribution of perivascular spaces, particularly at high fields, can provide new insights into pathological progression of vascular dysfunction in Alzheimer's disease and the interaction between vasculopathy and protein pathology. 7T high-resolution time-of-flight angiography enables the classification of individual hippocampal vascularization patterns, and support individual assessments of hippocampal vascular reserve [136 137]. Thus, by combining these novel metrics with classical quantifications like white matter intensities and cortical microbleeds, it may be possible in the future to establish a comprehensive vascular profile to complement molecular, structural and functional imaging for a precision medicines framework.

Multimodal imaging to test disease mechanisms

Multimodal studies combining PET ligands for metabolism, protein aggregation and neuroinflammation are particularly powerful to examine underlying disease processes. Early studies established the strategy of amyloid PET to confirm underlying Alzheimer's pathology before assessing neuroinflammation [108 138]. This is now commonplace in clinical trials of Alzheimer's disease and its precursor of mild cognitive impairment, to supplement clinical diagnosis and enrich cohorts.

The multimodal approach was extended to demonstrate associations between processes, such as neuroinflammation and metabolic impairment [139-141], or the co-localisation of neuroinflammation and protein aggregation in Alzheimer's disease [142], PSP [143] and FTD [22]. When used in combination, they can address the relative prognostic value of imaging markers, and elucidate the functionally relevant processes that would be priorities for disease modifying treatment [144]. Together these studies provide evidence for the interplay between critical disease processes, elucidating the cascade of pathogenic mechanisms.

Molecular imaging with PET can be combined with other imaging modalities that assess neuronal connectivity, including diffusion MRI, functional MRI and Magnetoencephalography (MEG). Neuronal populations are functionally and structurally connected at a number of scales, from microcircuits within a cortical column [145] through local, modular connectivity communities [146] to whole-brain networks [147].

While there is a high degree of correspondence between structure and function in the healthy brain, the same is not necessary true in dementia or other neurodegenerative disorders. For example, early synaptic loss and neurotransmitter deficits can alter function (cognitive physiology) without cell death (atrophy) [148 149]. The transition from pre-symptomatic to symptomatic stages of neurodegeneration appears to be more closely related to a loss of functional connectivity and information transfer in brain networks than a sudden change in brain structure [150]. In Alzheimer's disease this is reflected in close associations between tau burden and hippocampal function, irrespective of hippocampal volume [151], and a stronger relationship between functional connectivity

and memory than with atrophy [152]. Functional adaption may occur in structurally healthy brain remote from the site of neurodegeneration [153], or within areas of early neurodegeneration [154].

Seemingly contradictory and inconsistent reports of the relationship between brain atrophy and hypometabolism can be reconciled when considered at the network scale. For example, Weil, et al. [155] demonstrated that, while the published neuroimaging studies of dementia in Parkinson's disease did not show consistent effects when meta-analysed with traditional univariate methods, a network mapping approach revealed consistent dysfunction in a network centred on the hippocampus. Further, they showed that dissociable network abnormalities were associated with visual hallucinations and mild cognitive impairment, supporting a move away from views of neuropsychiatric abnormalities in Parkinson's disease as a unitary construct. Similar approaches have both reconciled similar controversies in Alzheimer's disease and highlighted the involvement of different connectivity networks across neurodegenerative syndromes [156].

It has been consistently observed in both the structural [157] and functional [158] 'connectomes' that those brain regions that are most densely connected are most vulnerable to neurodegeneration. The properties of these densely connected 'hubs' [159] can be quantified mathematically, for example with graph theory [160] or structural equation modelling [161]. These approaches have yielded novel insights into disease mechanisms in dementia, including vulnerability of long connections in Huntington's disease [162]; disease initiation in Alzheimer's [163] and mechanisms of hallucinations in Parkinson's dementia [164].

In models of Alzheimer's disease, hub regions may be vulnerable because they are most likely to receive pathological proteins that propagate trans-neuronally, in a "prion-like" manner [165-167]. Much as countries with highly connected airports are more vulnerable to epidemics, hub regions are more likely to receive pathology from 'seed' regions affected in early stages of the disease [168-172]. This hypothesis has been tested by combining PET ligands of protein aggregation and functional imaging of brain connectivity using MRI and MEG. The combination provides *in vivo* evidence for this process in humans that was only previously available in animal models [23 82 173-175], and allows probing of disease across temporal as well as spatial scales.

Although implicated in several neurodegenerative diseases, transneuronal spread may not be the only cause of hub vulnerability. Multimodal imaging studies have demonstrated that in Parkinson's disease, differential gene expression contributes [176] while, in progressive supranuclear palsy (PSP), higher metabolic demand [177] or reduced trophic support [178] may account for the relationship between protein aggregation and abnormal functional connectivity [23]. It is likely that differences in the ultrastructure of the pathological protein impact its propensity to traffic trans-neuronally [74], which may account for differences between widespread pathology in network-level diseases such as Alzheimer's and motor neurone disease (ALS/MND) and more focal neurodegeneration in PSP and semantic dementia, despite abnormal aggregation of common proteins (here, tau and TDP-43 respectively). Similar principles apply in synucleopathies, with different strains in MSA and LBD [179].

Relating neuronal properties to complex behaviours

Functional imaging can assess real-time connectivity between regions, principally based on data from fMRI, M/EEG or direct electrode recordings. These fall into two broad categories [180]: (i) 'Functional connectivity' describes activity between brain regions that is correlated over time or phase-coherent, reversing the Hebbian principle to state that neurons that are wired together fire together; and (ii) 'Effective connectivity' describes the application of techniques such as dynamic causal modelling [181] or Granger causality [182] to infer directed influence of one brain region over another.

In the healthy brain, the structure of connections is closely matched to the strength of their functional connectivity, set within overall cortical connectivity gradients [183] that span a range of spatial scales [184]. This applies both when the mind is at rest (the so-called 'resting state'), and when it is engaged in a task [185 186]. However, the same is not true in neurodegenerative disease. It is a consistent observation that the strength of resting-state connectivity between two brain regions falls as those regions are affected by neurodegeneration [187 188]. However, when those regions are engaged by a task, their connectivity can be paradoxically increased compared to healthy controls, perhaps in compensation as they work harder to perform a cognitive operation with a less efficient neural architecture [189 190].

Watershed models [191] use the analogy of a river and tributary system to explain how a large number of biological, psychological and social variables contribute hierarchically to the overall expression of disease. Intermediate stages of this hierarchy are termed 'endophenotypes', which can be observed as cognitive or neural properties. Such models can be powerfully applied to multi-modal neuroimaging data to explain properties such as fluid intelligence [192]. Furthermore, they can give an insight into what factors might mediate epidemiological observations; for example Ronan, et al. [193] demonstrated that the recognised association between mid-life obesity and late-life neurodegeneration can be accounted for by changes in white matter integrity. The concept of these models can be extended by the addition of a phenotypic "delta" at the end of the metaphorical river; recognising that multiple cognitive and behavioural outputs stem from different admixtures of common neuronal quantities. Multivariate analysis of large cohorts [194] can powerfully relate imaging and cognitive parameters, and can account for how this relationship changes as the brain ages [195 196].

In future, as larger and larger publically-available databases are generated, there will be an increasing role for big data informatics and 'AI' [197]. Such methods are already being applied to large repositories such as the UK biobank [198], which is collecting longitudinal neuroimaging of 100,000 participants, along with genetic, demographic, physiological, cognitive and behavioural data.

The way in which age and disease moderates the relationship between structure, function and behaviour is not linear. For example, in mild cognitive impairment hippocampal or entorhinal atrophy results in hyperactivation of medial temporal lobe circuitry, perhaps as inefficient compensation to rescue cognitive performance [152 199]. Such excessive local activity may act in a vicious circle to promote local amyloid deposition [200]. This may be a more general property of neurodegenerative disease, as highly active 'hubs' compensate for declines in structural connectivity by increasing their firing rate in early disease [201]. Later in disease this metabolically demanding compensation breaks down [202]. Cross-sectional studies relating neuronal connectivity to pathological protein deposition have been crucial to corroborating these hypotheses [23], and will be strengthened in future by large, longitudinal cohort studies employing multi-modal imaging. Overall, studies of this type can be extremely powerful in connecting symptomatology to neuronal dysfunction and disease pathogenesis, allowing both generation and testing of prevention and treatment hypotheses (figure 1).

Assessing microcircuit-levels in humans

So far, we have discussed the macroscopic level of brain structure and function, representing large neuronal populations and the major white-matter connections between them. We turn next to the microscopic level, where initiating events in the neurodegenerative cascade occur [1-4]. Neuroimaging is not blind to changes at this scale.

Ultrahigh resolution structural imaging with 7-tesla MRI can still be considered mesoscopic, being sensitive to functional and volumetric changes on the order of hundreds of microns (cf. a grain of sand). However, these field strengths are particularly sensitive to susceptibility changes, and as a result are able to detect microbleeds [203] that were previously only demonstrable at post-mortem [204]. Recent advances in laminar fMRI have opened up the ability to examine degenerative changes within specific layers and address mechanistic questions at a microcircuit scale [205-208].

Synapse loss correlates closely with symptoms in Alzheimer's disease [209], perhaps related to the direct synaptotoxicity of Amyloid and tau aggregates [148 210-213]. This is reflected in functional imaging, for example by tau-related reductions in fMRI hippocampal novelty responses [151], amyloid-related resting state alterations [214], and inflammation related changed in connectivity of the medial temporal lobe [215]. Amyloid pathology can also be associated with intrinsic neuronal hyperexcitability of pyramidal neurons [216]. This is paralleled by inhibitory dysfunction, which is thought to underlie the generation of network hyperexcitability and hypersynchrony that is observed in neurocognitive circuits of patients [217 218]. Within the hippocampus-cortical circuitry, synaptotoxic effects, hyperexcitability, compensatory hyperactivity and neurodegeneration are interacting on a very small spatial scale. Therefore, a combination of very high resolution structural imaging with meso-scale resolution fMRI can advance an in vivo understanding of these factors in humans and their temporal succession in the course of Alzheimer's disease.

The temporal resolution of magnetoencephalography provides the opportunity to assess the neurophysiological signatures of neurodegenerative diseases, most notably in terms of oscillatory dynamics. Neurodegenerative diseases are commonly classified by the site of pathology, which tends to track phenotype, but they also cause distinctive changes in the temporal structure of neuronal communication, both in the resting state [219], and when engaged in a task [220]. These changes can support disease classification even between patients in whom the localisation of pathology is the same, providing a first step towards single subject precision medicine approaches when therapies become available for specific proteinopathies.

The spatial resolution of imaging and image-based neuronal models can also be exploited. For example, in frontotemporal dementia there is non-uniform loss of cortical cells [221], with supragranular layers [222 223] and von Economo neurons [224] particularly vulnerable. Biophysical models, such as dynamic causal modelling (DCM) [225] can be applied to MEG/EEG [226] and fMRI [181] data, to make powerful inference about the state of the laminar-specific cellular populations, in cortical microcircuits [145 227]. When combined with pharmacological intervention, these techniques can assess dynamics that are specific to individual neurotransmitters and even receptor populations [228], allowing a precision of *in vivo* therapeutic assessment that was hitherto only possible with preclinical models of dementia.

Experimental medicine studies

Neuroimaging can enhance experimental medicine studies in several ways.

First, imaging biomarkers can be used as a screening tool to identify pre-symptomatic cases. Early intervention may be more effective to reduce the long term burden of disease, or even prevent symptom onset. For example, amyloid PET imaging is commonly used to identify those with Alzheimer pathology, either as latent disease in presymptomatic individuals, or to confirm Alzheimer's disease pathology as the likely cause of mild pre-dementia cognitive impairment and high risk of conversion to dementia [229 230]. There is a 3% annual risk of conversion to amyloid positivity in cognitively normal over 65s, and this increases to 7% in those positive for apolipoprotein ε4 [231]. These individuals show more rapid cognitive decline than their amyloid-negative peers [232]. This already provides an inclusion criterion for many clinical trials. However, screening for Alzheimer's pathology is problematic: elderly amyloid positive cognitively healthy individuals still only have an 11% annual risk of conversion to MCI or AD [233], meaning that trials enriched in this way would still take years. Tau imaging with the ligand flortaucipir may help to stratify such cohorts. Moving forwards, such imaging biomarkers will be increasingly important to identify pre-symptomatic pathology in those at risk of sporadic or genetically determined dementias, whether Alzheimer's disease [18 19] or FTD [16 17].

Second, neuroimaging provides an array of surrogate outcome measures that may change more quickly and be quantified with more precision and sensitivity than behavioural and cognitive measures. While rescuing imaging biomarkers is not sufficient without changing the patient's clinical course, it can provide evidence of a treatment's effect on brain and degeneration as a prelude to clinical endpoints in later phase trials [234]. Atrophy is most widely used in this way, the logic being that a treatment that slows atrophy has influenced neuronal survival and is more likely to be clinically effective that a treatment that does not slow atrophy. Volumetric MRI is not standard in clinical trials, and is often more sensitive than clinical endpoints [235 236]. Ultrahigh field imaging (7-Tesla MRI) increases the anatomical resolution and neurochemical sensitivity of MRI several times over, compared to 3T MRI [237]. For example hippocampal subfield volumes can be imaged with a resolution of a few hundreds microns [238]. Observational studies are now underway to determine whether this technological advance supports earlier or more accurate diagnosis.

However, atrophy as a result of extensive cell death is a very late process in the pathogenesis of dementias. Upstream events may in principle be more suitable for earlier intervention studies, such as the loss of synapses [114-116] and inflammation [22 142]. To test the relative performance of imaging biomarkers, against each other and against fluidic biomarkers and clinical ratings scales, requires a head to head comparison of assay performance in the same participants. To this end, the deep and frequent phenotyping study [239] is underway, to compare established and novel metrics of the presence of Alzheimer pathology, and longitudinal progression. Functional MRI, multiligand PET and magnetoencephalography are longitudinally assessed alongside behavioural measures, CSF, blood and saliva biomarkers.

Third, neuroimaging can test candidates for restoration of the neural mechanisms of aberrant behaviour in small-n studies, over short timescales. For example, Hughes, et al. [240] used magnetoencephalography to demonstrate that the frontal lobe neurophysiological signatures of behavioural inhibition were reduced in behavioural variant FTD. They hypothesised that this might be due to reduced serotonergic innervation [241], building on evidence that selective serotonin reuptake inhibition modulates response inhibition in preclinical models, healthy adults and other neurodegenerative disorders [242]. By combining the psychopharmacological challenge with magnetoencephalography, Hughes, et al. [240] demonstrated that citalopram restored the imaging markers of inhibitory control. No change was demonstrated in behaviour, either because of power of because, using the watershed analogy described above, serotonergic deficiency is only one

tributary to the river of behavioural disinhibition in FTD, alongside atrophy, loss of frontal oscillatory connectivity [219 220] and GABA-ergic depletion [127 243].

Fourth, by identification of the causes of heterogeneity, neuroimaging methods enable cohort enrichment and stratification at inclusion; and can provide *post hoc* explanations of variation in a treatment response. For example, the selective noradrenaline reuptake inhibitor atomoxetine was unsuccessful in rescuing response inhibition in an group of people with Parkinson's disease, but sub-group analysis revealed that the drug was effective in those with relatively more severe disease, and intact fronto-striatal white matter connectivity [244]. The preservation of cortical outflow tracts was proposed as necessary for behavioural function to be restored through following functional restoration 'upstream' in prefrontal cortex [245 246]. Such *post hoc* analyses of multivariate data can reveal effects from studies of heterogeneous populations, and develop protocols to predict individual responses to medication, i.e. personalised medicine [247]. The heterogeneity of a cohort can be formally dissected according to stage (severity) and phenotype. For example, the SuStaIn model uses machine learning to distinguish subtypes from progression of disease, against which treatment efficacy could be individually assessed [248].

Fifth, neuroimaging with novel PET ligands can be applied in proof of concept and dose finding. For example, inhibition of O-GlcNAcase reduces phosphorylation of Tau in mice [249], and has been proposed as a therapeutic strategy in Alzheimer's disease and Progressive Supranuclear Palsy. ASN120290 is a novel, orally delivered inhibitor of this enzyme that has completed phase 1 safety trials [250]. In advance of a phase 2 trial, a dose finding study is using PET to directly image enzymatic function *in vivo* in real time [251]. This novel approach will reduce the number of groups needed in phase 2 trials, a crucial advantage when dealing with rare diseases. Similarly, 11 L-[1-^{11}C] Leucine PET allows for *in vivo* quantification of the degree of suppression of the unfolded protein response in upcoming trials [121].

Finally, neuroimaging can add value to clinical trials of investigational medicines, to inform our understanding of disease processes, establishing a 'positive feedback' loop in translational research. Early and late phase studies can be designed in a way that they include longitudinal follow-up of large disease cohorts with both established and novel biomarkers [18]. The benefit of these approaches is increased by data sharing, which is now practicable even for very large file sizes, previously a limitation to open data for neurophysiological data in particular. Meta-analysis and repurposing has been facilitated by consensus formats such as BIDS [252 253] and infrastructure like the Dementias Partnership UK Portal. This will enhance the value of imaging data through open Data, meta-analysis and repurposing.

Big data and the advent of artificial intelligence

As computing capabilities expand, the concept of 'big data' evolves, but it generally describes information too large or complex to be analysed in traditional ways. Artificial intelligence and machine learning techniques applied to large, multi-modal datasets hold huge promise for the discovery of complex, non-linear relationships between pathological and environmental factors, improving diagnosis, prevention and treatment (figure 1). However, with larger-scale data one must be careful to minimise the risks of false discovery through statistical chance or hidden biases [197 254], guard against the over-interpretation of small effect sizes [255], and maintain interpretability in multi-modal analyses [256].

Big data may arise from a coordinated effort to obtain a standard set of measures, or to repurpose data generated for other purposes such as healthcare. The former is exemplified by the Human Connectome Project, with four hours' of imaging in 1,200 young volunteers [257], and similar

acquisitions in 1,200 older individuals, 1350 teens, 500 babies/toddlers, and 1500 foetuses [258]. A second example is the UK Biobank, which aims to acquire MRI in 100,000 individuals for combination with lifestyle, biomarker and genomic data [198]. Around 40,000 scans have been acquired to date.

Big data can also be built by fusion of smaller studies. Data sharing is now readily available, facilitated by infrastructure like the Dementias Partnership UK Portal [259], which enables research teams to deposit imaging and behavioural measures at medium or large scales. This facilitates replication and extension, and generation of very large cross-cohort analyses. Consensus data formats such as BIDS, initially developed for MRI [252] and now extended to MEG [253] make this process easier. Consortium efforts to accounting for differences between scanner and acquisition protocols such as ENIGMA are increasing our ability to pool inference across diverse cohorts, allowing meta-analysis and repurposing [260].

Big data hold particular promise for hypothesis generation, linked to bespoke studies for hypothesis testing. This reduces the risk of recruitment bias resulting in very large normative cohorts. For example, one must consider whether those with pre-dementia are equally likely to volunteer for a cohort study? Their numbers might either be reduced by latent cognitive difficulties or apathy, or increased by a wish to understand subjective complaints [261].

The simplest approach to the analysis of big data is the application of a standardised univariate method at large scale. However, critical effects may be multivariate, complex and non-linear. Assessing these complex effects is better suited to methods collectively known as Artificial Intelligence (AI). This umbrella term is not precisely defined, and describes a range of approaches from supervised machine learning classification algorithms like support vector machines [262], through to 'deep learning' efforts that apply multiple, increasingly abstract, processing layers [263]. Through such brute force associative techniques in large datasets, deep learning can achieve very high diagnostic accuracies for dementia [264]. However, these accuracies are vulnerable to over-fitting, sometimes give little insight into what disease mechanisms are driving classification, and can fall down if the classifier comes across abnormalities or variants it has not previously observed.

The application of big data approaches to dementia also raises a number of ethical considerations, beyond those of privacy, data security and governance common to all healthcare datasets [265 266]. Firstly, it may require a change in mind-set among clinical specialists, with hard-earned diagnostic acumen, to trust algorithms and methods that rely on interactions and hidden states that are not transparent. Secondly, the responsibility for inaccurate diagnosis would be unclear - a problem likely to be particularly challenging for rarer dementia syndromes. Thirdly, the social, financial and psychological consequences of making a pre-dementia diagnosis in the absence of disease modifying treatment are difficult to manage. The response to these challenges requires consultation beyond the neuroimaging community, maintaining a clear distinction between applications for research and direct patient care.

A roadmap to clinical trials

We are entering an exciting phase in dementia research, moving from observational to therapeutic studies, and validating preclinical models in terms of the mechanistic analysis of human dementia pathogenesis. Many novel therapeutic targets have been identified and diverse disease modifying agents are coming to clinical trials. Although the ultimate goal is to prevent cognitive and behavioural decline in a way that is meaningful for patients and families, and with health economic benefits, there is an intermediate stage of experimental medicine that will need to exploit quantitative imaging of neuronal and physiological function.

There are large, observational, longitudinal cohort studies with multi-modal assessment that serve as foundational data on natural history and biomarkers to inform evidence-based interventional trial design. Large-scale collaborative efforts such as the Alzheimer's disease neuroimaging initiative (ADNI) have changed the landscape by bringing together clinical, imaging and fluid biomarkers to feed into clinical trials. This prototypical study is now in its 3rd phase and expanded to include MCI [267]. It has set the stage for a large number of other collaborative international studies involving advanced imaging, clinical cognitive and fluid biomarkers, including the Parkinson's Progression Markers Initiative [268] (PPMI; ~400 patients with Parkinson's, 200 controls over 30 sites in 12 countries); the Genetic Frontotemporal dementia Initiative [16] (GENFI, ~1,100 people from families with familial FTD across 11 countries); ARTFL-LEFFTDS Longitudinal Frontotemporal Lobar Degeneration [17 269] (ALLFTD ~1,500 patients with FTD); the Dominantly Inherited Alzheimer Network Trial [18 19] (DIAN-TU, ~200 patients with familial Alzheimer's, specifically focussed on early-stage drug trials, with several thousand in the expanded cohort); the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing [270] (AIBL, ~1,000 aging individuals, some with AD or MCI); the DZNE Longitudinal Cognitive Impairment and Dementia Study study [271] (DELCODE, ~1,000 individuals with pre-dementia); the 4 Repeat Tauopathy Neuroimaging Initiative [272] (4RTNI, ~100 patients); and the Longitudinal Early-Onset Alzheimer's Disease Study [273] (LEADS, ~600 patients aged between 40 and 64).

As well as their multimodal imaging data, the open science framework (OSF) of these initiatives encourages collaboration, and replication and validation of findings. At an even larger scale, the ENIGMA consortium spans diseases and facilitates mega-scale imaging / genetic collaborations to answer mechanistic questions only possible with very large numbers of patients [274].

Complementary to these initiatives, observational cohorts are critical to deeply phenotype patients, using multimodal imaging and fluid markers. These enable bespoke, experimental and innovative elements to be included and often feed into larger consortia. For example, TRACK-HD [20] and TRACKON-HD [21] are a multisite observational cohort study of Huntington's disease. Alongside clinical and fluid biomarker data, advanced neuroimaging data are collected, including structural and functional MRI with graph theoretical approaches. Crucially, clinical trials of antisense oligonucleotide designed to reduce mutant huntingtin protein are underway [275] and neuroimaging metrics refined in observational cohorts inform long term trials of these and similar agents. Similar comprehensive multimodal observational cohorts have now been established across neurodegeneration: in Parkinson's disease (PD), the Vision in Parkinson's study collates retinal, visual, fluid and genetic markers with advanced imaging [276 277] with the aim of refining markers of progression in PD to stratify patients for clinical trials. The genetic frontotemporal initiative (GENFI)[16] is a multicentre observational study of people with or at risk of genetic FTD, focussed on imaging, cognition and fluid biomarkers. It has shown for example that in progranulin-associated FTD, white matter hyperintensities correlate with disease severity and plasma markers of neurodegeneration (neurofilament light) [278], providing target markers for forthcoming clinical trials.

This approach emphasises the value of early-stage feasibility trials to produce meaningful insights into disease mechanisms, paving the way for larger trials over longer time periods. For example, the AZA-PD study [279] is an early phase double-blind placebo-controlled trial of immunosuppression in early but high-risk Parkinson's disease, aiming to modify progression by reducing neuroinflammation. Azathioprine is a drug that exerts its effect slowly, and it is anticipated that efficacy as measured by traditional motor scores will be weak in an 18 month trial. However, by including repeated longitudinal PET imaging with the TSPO ligand PK-11195, and MRI, one can show proof of concept for the therapy.

Overall, intelligent design of the neuroimaging component of trials enables true proof of concept, illustrating feasibility and de-risking the process by providing early surrogate endpoints that enable

Go/Nogo decisions to longer-term cognitive and behavioural endpoints. Medical, scientific, and commercial considerations are complementary, but each enhanced by neuroimaging to work towards a cure for dementia.

Summary

Advances in neuroimaging are critical for the transition from discovery-science and drug-discovery through to effective and timely clinical trials of novel treatments for dementia and neurodegeneration. In this review, we have illustrated how methodological advances in PET, MRI and neurophysiology, linked to detailed disease models and AI analysis methods, can elucidate the pathophysiology of human disorders. Understanding of the causes of heterogeneity can in turn be applied to stratify clinical trials, and in due course to the realisation of precision medicine. Building on cross-sector collaboration and best practices for open science, advanced in brain imaging will enhance good clinical care and dementia prevention strategies.

Figures

Figure 1: A cartoon illustrating the ways in which neuroimaging can contribute towards prevention, diagnosis and treatment of dementia, as we work towards an overall cure.

Figure 2: A cartoon illustrating the levels and scales at which neuroimaging can help us consider pathology, between the underlying gene and cause and eventual clinical trials of investigational medicines.

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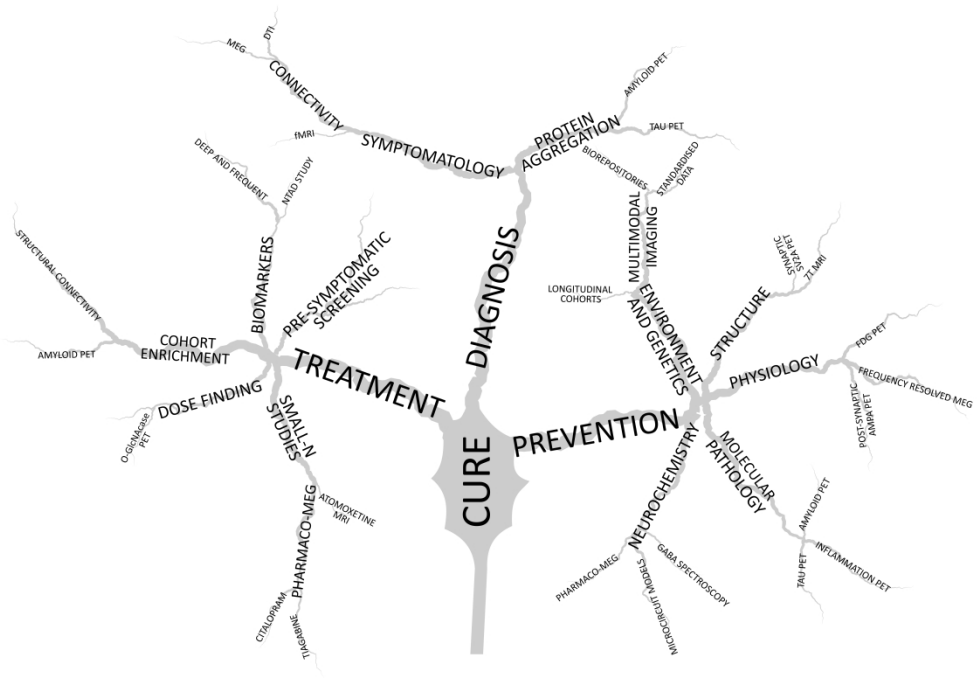
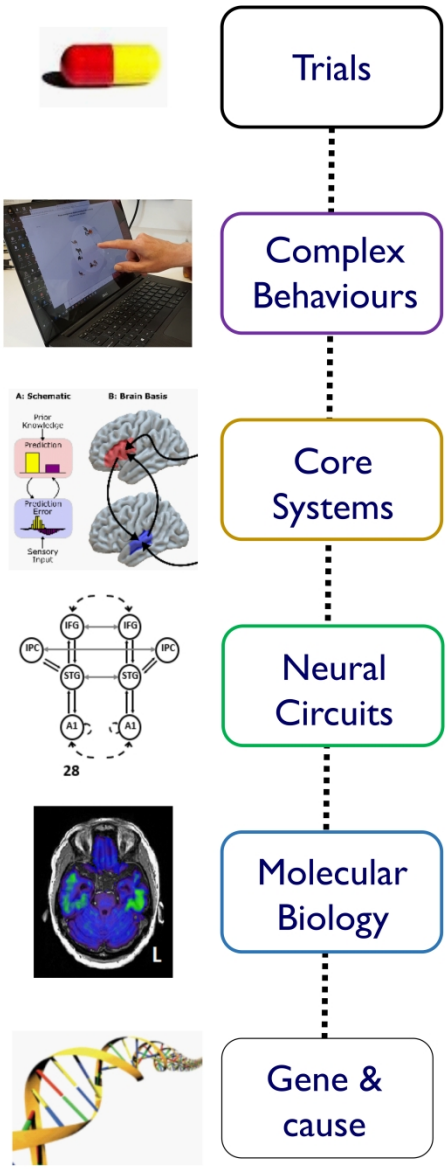


A cartoon illustrating the ways in which neuroimaging can contribute towards prevention, diagnosis and treatment of dementia, as we work towards an overall cure.



A cartoon illustrating the levels and scales at which neuroimaging can help us consider pathology, between the underlying gene and cause and eventual clinical trials of investigational medicines.