EDITORIAL

Alzheimer’s disease: time to focus on the brain, not just molecules

One of the biggest drivers for development of targeted treatments for neurodegenerative diseases has come from a better understanding of the molecular pathology. In Alzheimer’s disease, the impetus has been seismic over the last three decades, with a host of findings implicating amyloid or tau as key molecules involved in the process of brain degeneration (Ballatore et al., 2007; Braak and Del Tredici, 2015; Selkoe and Hardy, 2016). As a result of this pioneering work, there have been intensive efforts both to image amyloid and tau in vivo (Brosch et al., 2016; Thal and Vandenberghe, 2016; Villemagne, 2016) and to develop therapies aimed at these molecular targets (Godyń et al., 2016).

The likelihood of success for this strategy has been dealt a massive blow, however, by the announcement of failure of a series of trials over the past few years. This includes, most recently, EXPEDITION 3, a phase 3 trial conducted by Eli Lilly of solanezumab, a monoclonal antibody directed against amyloid-β. Over 2100 patients with a clinical diagnosis of Alzheimer’s disease were recruited. All were ‘amyloid positive’ on 18F-florbetapir PET or cerebrospinal fluid amyloid-β (CSF Aβ1-42). They were randomized to the drug or placebo for 80 weeks. In late 2016, the company reported that there had been no significant effect on the primary endpoint, the Alzheimer’s disease Assessment Scale-Cognitive subscale (ADAS-Cog14).

Although there were more encouraging effects on other measures, and there are also other antibodies that target amyloid-β which show promising results (Sevigny et al., 2016), many have taken this result to be a wake-up call. Is clearance of protein aggregates really ever likely to succeed in improving cognitive outcome? It would be wonderful if it was going to be that simple. However, given the long prodromal time course of most neurodegenerative conditions, including Alzheimer’s disease, might it not be surprising if clearance of a culprit molecule were to have any impact at all—more than a decade after it started to wreak havoc?

Perhaps the best that could be hoped for using this strategy is less progression of cognitive deficit. But for such an effect to be detected within just a year or two of starting a treatment, the methods currently used to measure cognitive function in this context are unlikely to be sufficiently sensitive. One important issue, therefore, is whether the ‘gold standards’ for cognitive outcome in clinical trials need to be replaced with more sensitive measures that are used in cognitive neuroscience research, such as those developed recently to probe short term memory (Liang et al., 2016; Rolinski et al., 2016). Another line of argument is that antibody trials need to start far earlier in the disease process to have an appreciable effect that can be detected by cognitive tests currently used in clinical trials. Hence, the ongoing attempt to treat individuals while they are still at an asymptomatic stage in a large Colombian kindred with autosomal dominant presenilin 1 (PSEN1) mutation Alzheimer’s disease (www.clinicaltrials.gov/ct2/show/NCT01998841).

The stark possibility remains though that no matter how early antibody therapies are introduced, they simply will not impact on cognition. Why might that be the case? Somewhere in the rush to target molecules, we seem to have put two very important issues to one side. The first is how the disease manifests: the variation in phenotype within Alzheimer’s disease. It is now abundantly clear that Alzheimer’s disease can present in very many different ways, with a range of cognitive and behavioural syndromes that varies widely across individuals. To date this phenotypic variation has not been a focus for the development of therapies, even though it might not be unreasonable to ask which manifestation of Alzheimer’s disease a new therapy might aim to improve. After all, cognitive and behavioural function is not one monolithic entity that can be captured easily by a single test score.

While one person with Alzheimer’s disease pathology might have episodic memory deficits without being afflicted by a behavioural syndrome such as apathy, another individual with the same disease can suffer from exactly the opposite pattern of deficits but have, in addition, other cognitive...
impairments, e.g. in the domains of visuospatial or executive function. Hence, the molecular similarity between the pathologies in these individuals is not an adequate explanation for their diverse phenotypes. There is no one-to-one mapping between molecule and phenotype. Instead the mappings are one-to-many: one molecule to many different phenotypes.

Conversely, many different pathologies can lead to the same phenotype. For example, the molecular changes associated with vascular dementia or Parkinson’s disease dementia can also lead to disturbances in episodic memory, visuospatial or executive function, apathy and so on. Thus the mapping is also many-to-one between molecular pathologies and cognitive or behavioural phenotype. Again, clearly, the molecular account is not an adequate explanation of how this might arise.

The second—related—issue that has been lost sight of, paradoxically, is the very organ we are dealing with. The ultra-reductionist approach offers an explanation of brain function at the level of molecular and cellular transactions. It completely ignores function at the systems level—of brain networks and the computations they perform, and crucially how these might lead to variations in phenotype. The complexity of the information processing system that is the brain and how that system can be degraded in very many different ways to lead to a diversity of phenotypes has largely been side-stepped in the drive to find a cure.

The gaps in levels of explanation, all the way from genes, molecules and cells through to networks and computations, and ultimately to phenotype are actually embarrassingly large. No wonder it is sometimes easier to skirt around them and hope that targeting the molecular changes will be sufficient. But it is now becoming abundantly clear that molecular changes lead to widespread network effects that can propagate far beyond the initial focus of pathology (Canter et al., 2016; Palop and Mucke, 2016). I am not thinking here about molecular dissemination, such as theories of prion-like propagation (Goedert et al., 2016). Rather, structural or functional changes at one point in a brain network can lead to long-range, distributed effects that can be broadcast widely to alter cognitive function and behaviour.

Growing evidence suggests, for example, that network level changes manifest as altered electrical activity can occur in both Alzheimer’s disease and mouse genetic models of Alzheimer’s disease (Roberson et al., 2007; Palop and Mucke, 2016; Vossel et al., 2016). Remarkably, both abnormal spiking on EEG and spatial memory deficits can be improved by levetiracetam, but not other antiepileptic drugs in an experimental model (Sanchez et al., 2012). These data suggest that components of Alzheimer’s disease pathology may predispose to epileptic—or epileptiform—activity which can propagate widely but might be amenable to treatment with an established drug. There are also ongoing studies that have attempted, with varying success, to examine the effects of deep brain stimulation on cognitive function in Alzheimer’s disease, presumably mediated by its widespread network effects (Mizadeh et al., 2016).

These are early days in the attempt to shift the focus from molecules alone to understand how molecular pathology alters brain function. To join molecular levels of explanation to phenotypic variation is clearly not going to be simple. The one-to-many and many-to-one mappings between molecular pathology and cognitive/behavioural phenotype outlined above make plain that we need an intermediate level of explanation. That level of explanation needs to account for how one pathology can produce a diverse range of phenotypes, and how many different pathologies can lead to the same phenotype. An obvious level of explanation that might fit this bill is at the level of brain networks. The phenotype would presumably depend upon the pattern of networks disrupted, regardless of the actual pathology affecting brain structural or functional connectivity.

In any event, there is sufficient concern about pursuing a narrow reductionist approach to warrant a wider, deeper discussion about the future development of therapies for neurodegenerative conditions. There are some important questions, such as the ones posed by the one-to-many and many-to-one mappings discussed above, which logically cannot be answered by the molecular approach. In the future, it might be valuable to bring together molecular and systems neuroscience expertise in the service of new approaches to the complexities of brain degeneration.

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References