Ist es tatsächlich nur eine Frage von Zeit und Geld, bis der entscheidende Durchbruch zur Heilung von Alzheimer gelingt? Oder muss die Forschung vielmehr eingestehen, dass sie sich in einer Sackgasse befindet? Unser US-amerikanisch-deutsches Autorenteam fasst die aktuelle Lage zusammen und fordert zum Umdenken auf: für ein neues Konzept von Alzheimer, das neue Forschungsfragen in den Mittelpunkt stellt und Menschen mit kognitiven Beeinträchtigungen nicht ausgrenzt.

Liebe Leserinnen und Leser: Sie finden hier die ungekürzte, englische Langfassung des Artikels „Am Scheideweg – Die Zukunft der Alzheimer-Forschung“ (*Dr. med. Mabuse* 191, S. 30–34).

Alzheimer’s Research: Does it have a future?

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Introduction

Alzheimer's disease (AD) research is at a tipping point. On one hand the still dominant but weakening reductionist model asserts that it is only a matter of time and money before we find a powerful intervention to either prevent or cure the condition by disrupting amyloid pathways. On the other hand a growing counter movement is seeing so-called “AD“ not as one entity to be fixed but as a heterogeneous syndrome that arises due to a variety of processes that affect people through their entire lifespan, perhaps called “Alzheimer’s diseases“ in the plural.

With many countries currently developing national strategic plans we are at critical juncture where the decisions we make with our increasingly constrained resources will shape the future our elders and even our species will experience. We prefer to view “AD“ not merely as a biological condition rhetorically used to acquire research funding, but rather as a social lever for considering how to address our own cognitive limitations about the power of science to understand the brain and aging.

Historical context

Examining the state of neuroscience in the world can begin with Germany as a microcosm of the bigger picture. After all, modern brain psychiatry initially emerged in Germany at the beginning of the 20th century. Dr. Alois Alzheimer, Dr. Franz Nissl and their boss Emil Kraepelin made notable contributions to our understanding of the neuropathology and nosology of psychiatric disease, and first categorized AD in Kraepelin's Psychiatry textbook in 2010. Other German-speaking figures such as Theodore Meynert, who trained many future leaders, were accused of looking under the microscope, seeing what they wanted to see and constructing elaborate mythologies of how the brain worked. One can ask whether the claims about the power of neuroimaging as seen through the new cell stains under a microscope in the late 1800s and beginnings of 1900s were as exaggerated as the claims that modern clinical neuroimagers are making about understanding brain processes with PET and fMRI technology in the early 2000s.

Current state of research

The current dominant reductionist model asserts that AD is a single condition characterized by definable molecular pathology: neuritic plaques and neurofibrillary tangles. This pathology is said to emerge from defective genes, and many mutations have been described that appear to cause the rare, young age of onset autosomal dominant forms. Genes modify the late onset forms as well, particularly ApoE, a gene associated with cholesterol transport and neuronal repair.

Those who carry one or two copies of the ApoE4 form are at increased risk for a severe case of brain aging due to a variety of factors including vascular ones. Moreover, ApoE4 is quite pleiotropic and affects risk for cardiovascular disease, macular degeneration and other conditions. Because the empirical foundations in different ethnic groups and theoretical modeling are challenging, it is not possible to give people precise estimates of their risk and therefore difficult to imagine genetic testing serving as the foundation for the world of personalized medicine as promised by the evangelical geneticists of our day.

Many of the genes under scientific scrutiny appear to affect the processing of a protein fragment called amyloid, produced by the amyloid precursor protein gene on chromosome 21. Portions of

this larger protein can be found in the center of the neuritic plaques and in small oligomers that are soluble. No one is quite sure what the normal amyloid or its precursor proteins do and which forms, if any, are toxic. However, this has not stopped nearly two dozen drug trials from being conducted over the past decade, all of which have failed to elicit cognitive or functional benefit, even in the cases where amyloid clearance has been achieved (interestingly, the recent anti-amyloid drug Semegascestat worsened cognitive decline in patients who took it). Attempts to image amyloid in life have been more successful. However, the utility of this procedure is unclear, particularly since people can have significant amounts of amyloid in their brains and not suffer from apparent dementia.

Most of the current generation of drugs do not act on molecular pathways of amyloid but rather at the level of neurotransmitters. The cholinesterase inhibitors provide very modest symptomatic benefit by acting through acetylcholine, one of the first neurotransmitters ever described. The effectiveness of these drugs in practice (rather than efficacy in trials) is very controversial as evidenced by the difficulties found in government decisions about whether to pay for such medications. No new drugs have been approved in several years and, as usual, the drug companies are tweaking their products around efforts to keep generics from consuming their large profits, for example the recently marketed 23 mg tablet of Aricept. The effects of these drugs on function and particularly quality of life are almost impossible to detect in most people. Some companies are trying to develop other drugs that act on neurotransmitter systems, particularly specific receptor subtypes. For example, drugs that act on nicotinic cholinergic receptors continue to be given some attention by the scientific community.

Clinical research continues to demonstrate the heterogeneity of what we now erroneously describe by the singular term “Alzheimer’s disease”. A large number of risk factors are being identified that involve diet, exercise, cognitive and psychosocial activity as well as environmental exposures across the lifespan. Commercial brain health computer programs are being promoted to prevent cognitive decline with brain aging, although limited evidence exists to support their benefit in daily life. Most clinical research has been focusing on the attempt to develop biomarkers, using body fluid measurements and neuroimaging. Most of these attempts have focused

either on measuring loss of nerve cells – for example atrophy on MRI – or specific amyloid and tau markers in CSF or PET scanning. Although measurements can be made, variability is considerable and the overlap among symptomatic, partially-symptomatic and asymptomatic groups makes it difficult to use the test clinically.

New proposed diagnostic criteria in the United States and Europe emphasize biomarkers and deemphasize clinical symptoms and even autopsy. Consequently, one can now be diagnosed as having asymptomatic "AD" on the basis of biomarkers or as having mild cognitive impairment (MCI) without dementia (dementia is defined by cognitive impairment associated with problems with activities of daily living). Mild cognitive impairment has recently been divided into early and late forms, which continue to clearly demonstrate a continuum of brain aging changes rather than discrete stages. In addition to efforts to change our criteria for AD, the DSM-V (due out in 2013) is proposing to eradicate the word "dementia" from the manual altogether and replace it with "neurocognitive disorder of the major and minor types". However, this proposed change is controversial and presently being challenged.

Other clinical research continues to show overlap between the different forms of dementia. For example it has been increasingly difficult to differentiate degenerative dementias from vascular causes as AD has features of both. Once again, this serves to demonstrate the enormous heterogeneity and overlap in dementia disease categories. So too do overlaps between so-called AD and frontal lobe dementia and Parkinson's disease also exist. Our efforts to use molecular and imaging approaches to clearly subtype forms of dementia seem to yield patterns that are of limited use clinically. We still cannot tell specific patients much helpful information about prognosis or appropriate therapies.

The most notable feature of clinical drug trials in AD has been the repeated failures to find any effective therapies. The field wants to move towards prevention, which means early identification of the people most at risk. But studies to demonstrate that slowing progression of disease or even preventing the deficits of the conditions are complex, expensive and ethically questionable. We have little idea about what drug to try in the intricacy of the multi-system decay we observe in AD. Consequently, the most effective intervention may well be a multifaceted brain health

program that could well apply to everybody since, from womb to tomb, we are all at risk to one degree or another for aging associated cognitive decline. Indeed, as we have seem obsessed with the reductionist idea of amyloid as "the" answer, the bigger picture has been neglected and regrettably, the clinical results of this restricted vision have been disappointing. Funds to study the intricate multi-systemic and environmental interactions that lead to dementia should be a priority as well as the development of brain health interventions.

However, a new force is emerging in clinical research which is based on a broader conception of so-called AD(s). The conditions are increasingly viewed as severe forms of brain aging, which are caused by a variety of factors that act on an individual's brain throughout his or her entire lifespan. These factors can include exposure to environmental toxins like lead and mercury as well as head injuries received in sports or warfare, inappropriate nutrition and the gradual impact of stress and depression. With these more "ecological" models, it is avowedly more difficult to prove with the same degree of certainty – as can be found in a test tube or animal model – the specific hypothesized causal links particularly in an individual patient. However, in the absence of clear and convincing data it still seems commonsensical to apply public health measures towards lifelong brain health measures. Longitudinal studies on religious groups such as nuns and Seventh Day Adventists provide the most compelling evidence that brain healthy behaviors across the life course can lead to better downstream outcomes.

The humanistic interpretation of our current state of research is that people with dementia ought to be viewed on a continuum inclusive of all of us rather than as a separate category of person altogether. This type of approach leads to models of solidarity, and can help Western countries move beyond current dehumanizing models. Indeed, viewing brain aging as a "disease-event" called "AD" has led to the creation of exclusionary labels, categories and popular language that separate "normal" functioning people from those with dementia.

Rather than seeing ourselves on a continuum with those more severely affected by brain aging, we now sort these persons into disease boxes based on arbitrary diagnostic thresholds, and extend stigmatizing mental illness labels onto them. These labels are freighted with ominous cultural meanings: We consider those with AD "disease victims", "lost selves", "bodies that have

left the mind behind" and even "zombies", treating them as the living dead – walking corpses to be both pitied and feared, despite their obvious signs of life. As such, aging persons in our culture suffer not only from neurodegenerative processes, but also from the anxieties of a hypercognitive culture that is often dismissive, if not contemptuous, of those with memory problems who are furthest downstream. The world should not be divided into two groups of people – those with AD and those afraid of getting "it".

Rather than promoting the aforementioned "zombie model" that frames dementia as a totalizing "loss of self" and depicts modern communities as being overrun by the living dead, a more humanistic model suggests that communities can be adapted around a story of greater solidarity, and creatively provide for the needs of those with cognitive challenges. The question we must all ponder is: How can we develop dementia-friendly spaces in our communities that enable persons more profoundly affected by memory loss establish meaningful relationships within the protective social networks of local communities while both enjoying and adding something of value in their neighborhood?

Around the world, persons with dementia are already becoming involved in group-based community storytelling (see Anne Basting's TimeSlips initiative at www.timeslips.org), visits to art museums (see programs for persons with dementia at museums in Stuttgart, Duisburg und Bremen, New York and Paris), and even going to school with children at places like The Intergenerational School in Cleveland (visit the school at www.tisonline.org). The campaign "Dementia friendly communities", exclaimed by the Aktion Demenz in Germany has led to impressive results within only few years: corresponding initiatives are active in many hundreds of municipalities (www.aktion-demenz.de).

The Future

One countervailing narrative for the future that challenges such revaluing of persons with dementia insists that we must invest more money into basic biological research on AD. The implication is that if we did find a cure we will solve our social problems. We do not ask what a cure would even look like. Do the molecular AD experts think we will "cure" brain aging so that

people will live until their bodies wear out with brains still functioning as they were when the person was young? We doubt that is the claim, but it still seems that they do not specifically address what a cure would actually leave society with in terms of cognitive aging. This model is promoted most strongly in the United States where people have a false and dangerous "positivist" belief that technology can fix everything if we just have enough movie stars, genes, politicians and money in the equation.

In fact, out of desperation, people now are exaggerating the claims that we can "fix" neurodegenerative diseases in one large group by using similar molecular approaches. A common example of this idea is that all neurodegenerative diseases involve protein misfolding problems. Genes produce proteins as simple linear chains of amino acids, but in order to function they need to develop secondary and tertiary shapes. In some diseases such as the rare prion conditions caused by a proteinaceous infectious particle, protein folding does seem to play a clear role and different mutations clearly interact with environmental exposures. There is no doubt that some synergies can be created by examining processes in different conditions in which nerve cell loss is characteristic. Germany has pursued this endeavor by forming the new German Center for Neurodegenerative diseases but so much of the funding is going into molecular approaches alone.

Although many centers in Germany – for example Frankfurt am Main and Munich – are pursuing clinical research in the recently "new" but now increasingly outdated model, i.e. biomarkers and clinical trials, some sage German molecular biologists are beginning to have second thoughts. Konrad Beyreuther was one of the pioneering molecular biologists who once celebrated the power of science to eventually cure conditions such as AD. Now as Director of the Network Aging Research at Heidelberg University, he has come to conclude that molecular approaches are more limited than he had previously thought. With his permission, we quote him as saying: "Molecules are more or less the same in all human brains. But human brains are not at all the same." Konrad Beyreuther also told us that he now believes that the disease conceptions invented by scientifically-oriented doctors are of limited help to people who have cognitive impairment as they age.

Alzheimer's research is generally speaking equated with basic neuroscientific research. Huge funds are applied to these approaches, regardless of how clinically irrelevant the approaches may likely be not only in the short-term but the long-term as well. Although an increasing number of scientists consider the amyloid theory generally disproven or at least profoundly unproven today, the extensive funding of corresponding research projects carries on. But can we expect companies and research institutes, which have committed themselves economically to a field of research on a long-term perspective, to concede a miscarriage of an approach, instead of continuing to demand for funding? Most likely the answer is: "No."

But who is it to put judgement on spirit and purpose of research projects? Who monitors how the economic resources of our societies are invested? The call for democratic control of science by the Austrian philosopher and theorist of science Paul Feyerabend is most relevant to our concerns. Scienticism, the religion of science, is the practice of a powerful few, but the practice, guidance and benefit of science should be the province of many. In the extended ecological understanding of brain aging, which we have outlined in this article, formerly marginalized questions become the focus of critical interest in research. One of these questions is, for example, which changes can be made in the environment so that people with cognitive challenges can stay in their community as long as possible.

Inspired by the person-centered movement in Great Britain, Germany is in a process of redefining the role of so-called AD or dementia patients: They are no longer reduced to passive objects of provision and become more and more subjects, who articulate their interests and demands in several ways (http://www.demenz-support.de/arbeitsfelder/teilhabe_und_gesellschaft). However, the scientific community has not taken this change of perception to heart yet. Whereas in countries like Great Britain person-oriented research and active participation of people affected by dementia has been discussed and promoted for several years now, Germany has only begun this conversation. But it is clear, that to address these new questions AD's research needs to involve people with aging brains.

And so we conclude with a quotation from another famous German philosopher:

“When a science appears to be slowing down and, despite the efforts of many energetic individuals, comes to a dead stop, the fault is often to be found in a certain basic concept that treats the subject too conventionally. Or the fault may lie in a terminology which, once introduced, is unconditionally approved and adopted by the great majority, and which is discarded with reluctance even by independent thinkers, and only as individuals in isolated cases.” (Johann Wolfgang von Goethe)

With those luminously relevant words, we join the free thinkers and deep ethicists to cast off the fetters of the language that have, for much too long, been imposed upon us by those driven by fame and fortune rather than a vision for human solidarity.

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