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Published in:
Acta Scientiarum Lundensia

2018

Document Version:
Förlagets slutgiltiga version

[Link to publication](#)

Citation for published version (APA):
Brun, A. (2018). Alzheimer's and other neurodegenerative cognitive disorders. A strategy to find cause and cure. *Acta Scientiarum Lundensia*, 2018(006), 1-11. Artikel 2018-006.

Total number of authors:
1

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Volume ASL 2018-006

Citation: (Acta Scientiarum Lundensia, ISSN 1651-5013)

Brun, A. (20018). "Alzheimer´s and other neurodegenerative cognitive disorders. A strategy to find cause and cure." Acta Scientiarum Lundensia (ISSN 1651-5013) **2018**(006): 1-11.

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Alzheimer's and other neurodegenerative cognitive disorders.

A strategy to find cause and cure.

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Abstract.

The aim of this treatise is to sketch out a strategy how to find a cause and cure for cognitive brain disorders and then primarily Alzheimer's disease (AD) based on recent and little explored research progress. Step one is to find the cause. Recent evolution has supplied the human brain with new astrocytes which regarding their remarkable properties can be expected to harbor the cause of AD and several other cognitive neurodegenerative disorders. Plausible causes have already been proposed and will be accounted for in what follows. A cause proved or made plausible provides a good ground for finding a therapy. We must also be able to diagnose the disorder at an early stage ahead of widespread and severe brain damage for a treatment not to leave behind a crippling condition! This possibility appears now to become a reality since recent research has identified the same changes in the retina as in the brain. They can there be diagnosed with modern ophthalmological techniques and appear long before brain damage produces symptoms during the several decades long silent phase when AD is under way. After arrest of the disorder the neuronal plasticity can be expected to deliver repair, more the earlier the disorder is arrested.

Research on Alzheimer's disease

The research on Alzheimer's disease (AD) took off November 1906 with Alois Alzheimer's report of a case with "A peculiar severe disease process of the cerebral cortex" (Alzheimer, 1910, Alzheimer, 2006, Hippus and Neundörfer, 2003). It was then regarded as unusual, merged with Mb Pick into a hybrid Pick-Alzheimer or drowned in a plethora of conditions regarded as caused by cerebral arteriosclerosis. Nowadays, this latter form, called vascular dementia or vascular

cognitive disease, stands for about 25% of cases and frontal lobe dementia for about 10%. Others are cognitive diseases related to Lewy body or Parkinson's diseases. The dominant is, however, AD with about 50% of cases. It has been predicted to increase dramatically in the future with an ageing population, a prediction which, however, has already begun to be modified. I have shown that the disease extremely often is complicated by vascular damage with complete infarctions, i.e. focal areas of stroke. A special contribution here was that I could show that there are also milder injuries due to temporary lack of circulation in white matter which "only" resulted in regionally more or less damaged brain tissue i.e. incomplete infarcts that selectively hit white matter why I called them selective incomplete white-matter infarction, SIWI, later by others also named White Matter Lesions (WML) or Leukoaraiosis. Widespread such damage can give a form of dementia that I called the white dementia. These two circulatory injuries frequently add to the symptoms at AD, in an individually different way why one case clinically often differs from another in several respects. This frequent companionship to AD justifies a supplementation of present or future treatment of AD directed preventatively against circulatory injuries. I also mapped the loss of contact points (synapses) in different cortical regions in normal aging, AD and at frontotemporal dementia (FTD). This is a disease for which I defined and clarified the pathology in the mid-seventies, which was later rewarded with international and Swedish prizes (Brun, 1987), and several further papers e.g. (Brun et al., 1995). When mapping the synapses, I could show that AD as opposed to frontal lobe dementia usually for long spares the frontal lobes with less synapse loss there. Synapse loss is by many considered to be the earliest and clinically most significant damage in AD and several other cognitive diseases. Here we have a large yet unexplored research field in the form of a host of newly discovered proteins in the synapses with obvious potential importance for nerve cell signaling, normally and in cognitive diseases and thus also for the search for a cause of AD.

Amyloid has for long dominated research.

Early on, it was found that AD closest to obligate complicates Down's syndrome which in most cases has an additional chromosome 21, i.e. additional gene material that regulates the protein substance amyloid, which inspired further mapping of mutations in the Alzheimer genome. This was supplemented with a whole range of other gene mutations, several linked to amyloid beta turnover. In

the last 40 years, research has therefore focused on amyloid as the cause of the disease. Amyloid is deposited in various forms in the brain in AD and it has been studied increasingly fractionated with the hope that this will reveal the cause of AD. This has not so far been crowned with success but has attracted enormous costs to the detriment of research on alternative causes. Attempts to vaccinate against the endogenous amyloid led to severe autoimmune brain damage as one would expect. Many treatment studies sponsored by several large pharmaceutical companies have recently been closed down for lack of results often as late as in phase three. Many other substances have also been topical, ranging from aluminum to micro-organisms such as spirochetes to name but a few. They have never been shown to trigger the disease but may never really have got the chance in competition with the priority hypothesis about amyloid beta etiology. However, for the pathogenesis i.e. the progression of the disease after start, amyloid may be of significance.

Modern Evolution the astrocytes

So far, all research has focused on the nerve cells which even a few years ago were considered the only cells that could cause cognitive diseases, but not astrocytes. The finding that astrocytes are essential for the existence and function of nerve cells has swung the pendulum to the nearest opposite and the astrocytes are now thought to harbor the cause of AD and several other similar diseases! Following occasional reports already in the nineties about previously unknown properties of astrocytes, there opened around 2010 a huge field for research after the discovery that evolution has provided the human brain with new cells. These are glial cells named astrocytes, cells that have previously been considered simple supportive cells but now by evolution provided with a multitude of properties almost as in neurons and therefore now classified as completely new cells. In a few years, some fifty articles were published on this theme. They may here be represented by Alexei Verkhratsky et al 2018, a late and comprehensive article on the subject, rich in references (Verkhratsky and Nedergaard, 2018).

On closer examination of older literature there are new thoughts about astrocytes usually based on morphological studies, but without today's knowledge of their functions. Already 1894 studies were performed by the early giant of brain research, the Swedish researcher Gustav Retzius (Retzius, 1908, Retzius, 1914), and in the first year of the twentieth century by Santiago Ramón y Cajal, (Cajal,

2014) (who shared the Nobel Prize in Physiology or Medicine 1906 with Camillo Golgi). These astrocytes have not been found in our evolutionary predecessors, and especially not in the test animals rat and mouse usually used as model animals for Alzheimer research. It is thus a doubtfully adequate disease model to draw conclusions from to a humane situation. This can be indicated by the finding that human astrocytes transplanted into rats make animals smarter! Not even chimpanzees have been endowed with more than a fraction of this evolutionary novelty. Thus, it is no longer the case of a few simple support cells but sophisticated cells that are far more plentiful than the nerve cells and form a communicating network spanning the whole brain. It cooperates closely with the nerve cells through a multitude of dendrites which enclose the nerve cells and their branches and talk to them in particular at the synapses. They are a prerequisite for the survival and function of the nerve cells. For example, astrocytes take care of a very selective supply of nutrients from the blood to the nerve cells and also removal of garbage in the opposite direction, i.e. the disposal of waste products formed by nerve cell metabolism. They also have the ability to signal in the first place with the transmitter glutamate. They record all incoming signals on their way to the nerve cells from all sensory cells in different parts of the body. They therefore harbor messages that tells you in what situation you are, i.e. how it feels in different parts of the body and also holds memories such as what you are interested in, want and can accomplish. This, together with the registration of all impressions from the sensory organs flowing into the brain and its neurons is thought to represent our consciousness, and even the soul! To avoid accusations of blasphemy, I should perhaps here reserve the spirit for the clerical profession.

New findings suggest mechanisms for the cause of neurodegenerative diseases.

Experimental studies show damage to astrocytes with atrophy very early in the course before amyloid and plaques accumulate but with retained number of astrocytes. This suggests a loss of essential astrocyte functions leading to pathological changes with loss of synapses, which they normally both initiate and maintain. In addition, the capacity to clear amyloid is lost which therefore accumulates, which all may contribute to cognitive impairment. Astrocytes in cooperation with nerve cells also control microcirculation, which can therefore

be distorted and lead to degenerative changes. The changes in astrocytes are said to be positively affected by an enriched environment (Verkhatsky et al., 2016).

The new system of astrocytes may suffer from weakness because it is phylogenetically very young which spells vulnerability. It is new and not yet sharpened and tested why, ironically enough, it could more easily fall prey to degenerative processes and thus trigger cognitive diseases through neglect of their nerve cell care. It has also been advocated that this could be due to an injury to astrocytes triggered by protein substances (cytokines) produced by microglia cells (Liddel et al., 2017). This remains to be convincingly proved and requires at least one additional background factor that activates the microglia. Microglia cells are not original genuine nervous system cells, but lymphatic cells immigrated in fetal week 11 when the vessels invade the brain and still have an immature blood-brain barrier with inadequate border surveillance that permits such immigration. The importance of mutations in astrocyte and microglial genomes is yet another relevant and little explored field for the pursuit of the search for the cause of AD.

Other evolutionary steps.

This astrocyte evolutionary step is complemented by another step I found during my research years at Harvard in Boston, USA, in the early sixties and presented as my dissertation thesis in 1965 (Brun et al., 1995, Liu et al., 1996). It was the recruitment of neurons from previously unknown sources and with a different migration route than the usual radial out from the generation zone around the ventricular system. These cells migrate in a cell dense stream of immature neurons down the base of the frontal lobes to the region of the olfactory trigone and then turn tangentially out over the cortical surface underneath the innermost cerebral membrane the pial membrane why I called it the Subpial granular layer (SGL) (Brun, 1965). These cells appeared to then turn inward into the cortex, also in accordance with other, later scholars' views, to form small interneurons, important for the associative functions. Especially the migration route makes these cells different from the rest as the different migration creates opportunities for completely different connections during the passage of other nerve cells and for the wire network in the outer layer of the cortex, the molecular layer. A similar migration has previously been known to occur in the cerebellum but not in the telencephalon. The relatively young phylogenetic age of these cells may signal

vulnerability and make them a likely starting point for the degeneration in FTD.

It is evocative to now again confront evolution in the form of a new type of astrocytes. One then anxiously wonders whether evolution has taken further steps that we have not discovered, and which further removes us from our predecessors including the rats and mice we use as experimental models and draw conclusions from. It may also alter brain processes compared to those in experimental animals in a way difficult to understand for researchers or can result in immature weak points because of a late phylogeny. The incentive for such steps in evolution can be assumed to be new demands on brain functions by the environment. Obviously, the brain is not just what meets the eye in the microscope but also has a built-in readiness and capacity to supplement the tissue structures according to new needs. A mild feature of this is the brain's distinctive plasticity with the ability to repair and supplement old neuronal equipment and create new contacts and signal pathways if necessary. This can be called a form of environmental every day evolution especially if the inheritance of acquired properties takes place, which is now by many thought to be the case.

The new astrocytes with a host of new features and functions in intimate interaction with the nerve cells is a huge yet largely unexplored research field as well as the aforementioned numerous protein substances in the synapses. As the nerve cells for their function and survival depend on the astrocytes, it lies very close at hand to seek a cause of the degenerative diseases type AD in these cells but also for several other degenerative diseases, as well as psychiatric disorders, something already discussed in the literature (Elsayed and Magistretti, 2015). Never have we had greater reason to expect crucial breakthroughs around AD and other brain diseases with access to these huge unexplored fields. As we find the cause or causes, we are on a far safer basis than ever for realistic research into a therapy.

Then needed is an opportunity to diagnose the disease before it has caused so much brain damage that therapy only permanent a severe defect condition, although some repair should take place from the remaining nerve cells. You do not get more cortical neurons during life as previously thought but do not lose as many as assumed based on computerized counting of nerve cells. The computer has probably misjudged atrophic neurons for glial cells as they are smaller than the definition of a nerve cell specified to the computer! Persistent atrophic nerve

cells can be of importance if the disease can be stopped since these cells may very well through neuronal plasticity have regenerative capacity left.

Alzheimer in the mirror of the soul

AD involves not only the brain where it gives rise to a series of relatively specific changes. The disease has a phase-up for several decades before the brain's reserve capacity is so depleted that the disease causes symptoms. The same changes spread very early to the retina of the eye, the mirror of the soul, which is a protrusion of the nervous system from the brain with nerve cells of the same kind as in the brain (Masuzzo et al., 2016).

It is now possible to diagnose these changes in the eye with new technology, thus making possible an early diagnosis long before symptoms from the brain, which is thus still relatively mildly involved. The neuro ophthalmologist will be a key figure in the diagnostic work. The eye has been called a window to the brain. The retina of the eye thus shows plaques with amyloid as in the Alzheimer brain, probably earlier than in the brain. They can be demonstrated with noninvasive retinal amyloid imaging. There also forms in the interior of retinal nerve cells neurofibrillary tangles destroying their transport system. It is also possible to register in the eye the equivalent of the EEG of the brain namely the Electroretinogram (ERG) which gives an idea of disease related dysfunction of the (glutamatergic) synapses in the retina. The blood flow is reduced possibly due to the deposits of amyloid in the walls of the vessels just like in the brain. These changes go with a progressive thinning of the retina, nowadays routinely recorded, in pace with the advancement of the disease in the brain. This is the change that is easiest to relate to early reading difficulties and also disturbed perception of color. This is likely not triggered by brain damage since the visual cortex is usually late and not very severely involved in most cases, but more likely caused by the degeneration of the retina! We could here have an instrument for screening of the disease in the population as well as an opportunity for early diagnosis, well ahead of brain symptoms and more advanced brain damage. A presently somewhat unclear question is whether in the retina there also are new astrocytes analogous to those in the brain. This would be reasonable since the nerve cells on their migration into the retina should have demanded the company of their vital caring astrocytes. If they reach the retina, they could more easily be studied in vivo here with the aim to find the changes they undergo, and which

could be linked to the emergence of related nerve cell damage and the accompanying cognitive disease! Research on astrocytes must be performed in humans since sporadic AD is not present or cannot be reproduced in animals and 99% of AD cases are of that type. If the astrocytes can be studied in the retina it would facilitate the search for an astrocyte related cause of the disease and the search for a cure for the brain but also for the retina. One can then also in the retina study which treatment that gives the best individual results.

Sustainability of Research results.

Many of the basic findings here are well founded and would likely pass the test of time. Truths otherwise come and go in the world of science, such as the one we have comforted us with for a few years, viz. that we are getting a host of new neurons throughout life. This was refuted in an article in Nature 2018, one of the most renowned medical journals (Sorrells et al., 2018). A month later a reply was published saying that even older people get new nerve cells (Kempermann et al., 2018). This, however concerns only the hippocampus, a relay center for recall of memories. The ability of these new cells to function is dependent on their cooperating nerve cell centers for memory storage around the brain being healthy and there we get no new neurons. So, the question is perhaps mostly of academic interest in the case of widespread cognitive degenerative brain diseases. There are other doubts about the integration of these new nerve cells into the nervous system. They suffer from genetic errors of the same kind as their diseased predecessors they are set to replace and are also completely inexperienced. This should apply also to stem cells, the transplantation of which has now been given the go-ahead in Japan 2018 (Inacio, 2018). But that the hippocampus gets new neurons have I always considered plausible, since this center was originally intended for the recognition of fragrances. It is therefore directly exposed to the outside world via the nose and therefore also encounters the neurotoxic substances of the environment such as various heavy metals, which a colleague and I have demonstrated at this site (Brun and Brunk, 1973).

Future Evolution

Then you wonder what the next evolutionary step might be since there is reason to expect such readiness to be programmed. Something for the moment to wish for would be an addition to and stabilization of already established late evolutionary features such as frontal lobe structures in different respects. Frontal lobe social functions are those that the environment specifically increasingly plays on. The frontal lobe is also the evolutionary newest part of the brain and is therefore during life for long immature and with prolonged fine structural maturation up to about 40 years of age and therefore vulnerable. It also has an inter-neuronal cell population mentioned above that is evolutionary relatively new and has probably not yet found its final constitution, perhaps primarily regarding its ability to interact with the even newer astrocytes. Something the evolution should also take a closer look at is how the circulation in the white matter of the frontal lobes is dimensioned. The frontal lobe seems to have outgrown its basic vascular supply plan which now appears deficient with scarce, long vessels without shunts, a vulnerable arrangement. This paves the way for the aforementioned incomplete infarctions which are most common in frontal white matter. The new astrocytes may as newcomers in the brain also need stabilizing modifications. Otherwise, they could ironically enough cause the increase in the AD frequency now recorded, by failing in their care for the nerve cells and so increase the propensity for degenerative cognitive disorders for generations to come!

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