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ORIGINAL PAPER

The Earlier the Better: Alzheimer's Prevention, Early Detection, and the Quest for Pharmacological Interventions

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Abstract Although the risk factors, biomarkers, and medications for Alzheimer's disease appear to be almost identical in 1993 and 2013, profound changes can de detected throughout this time period. This article maps these recent changes in the conceptualization of Alzheimer's disease, especially the emerging trend toward prevention. While some preventive practices (e.g., brain training) and the search for early signs and biomarkers (such as APOEε4) have existed for a long time, the recent broadening of scope to include cardiovascular risk factors and their prevention, paired with pre-symptomatic detection of disease-specific biomarkers, has considerably impacted the conventional understanding of this syndrome and the possibilities for pharmacological and non-pharmacological interventions. The rationale for emphasizing multiple logics when explaining these changes is to avoid simplified argumentative pathways that exist among some scientists.

Keywords Alzheimer's disease · Prevention · Cardiovascular risk factors · Biomarkers · Early detection · Embeddedness · Multiple logics · Pharmacological interventions

Two Decades, One Question

In 1993, two Swiss researchers published an article asking: "Is prevention of dementia possible?" (Ermini-Fünfschilling and Stähelin 1993). Twenty years later, a group of North American scientists chose a similar title for their publication: "Can we prevent Alzheimer's disease?" (Carrillo et al. 2013). Both questions appear at historical moments wherein the available medications, but also the main risk factors and biomarkers—both important considerations in the field of prevention—seem to

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be almost identical. Despite these evident similarities, the direct comparison of these two periods (1993 and 2013) reveals profound conceptual changes within the context of Alzheimer's research. The question as to what these changes mean for pharmaceutical interventions is at the core of this article.

Many social scientists rightly emphasize the major role the pharmaceutical industry plays in the shaping of disease categories and treatment options (Healy 2012; Applbaum 2012; Oldani 2009; Angells 2004; and many others). I want to suggest here, a framework that does not neglect the profit-oriented forces stemming from "Big Pharma," but rather, one that also focuses on the multiple socio-historical factors that inform and enable pharmaceutical reasoning. This framework—the "embeddedness of scientific knowledge"—borrows from Mark Granovetter's (1985) classic article the idea that economic lives are based on complex social relations, and further, that truth claims are often linked to the ability to transmit trust.[1] Daston (2000, p. 13; see also Latour 2000) further elaborates on the concept of "embeddedness" and notes that "scientific objects … grow more richly real as they become entangled in webs of cultural significance, material practices, and theoretical derivations."

Thus, the emergent focus on prevention in the conceptualization of Alzheimer's disease cannot simply be seen as "pushing" by the pharmaceutical industry. Health-related facts are indeed "invented" and become increasingly part of what João Biehl (2006) has called "pharmaceutical governance." However, new insights and explanatory frameworks in most cases only emerge when based on existing theories and logics that can then get pulled and twisted, because of economic interests, but also because of the competitiveness and careerism among the increasing numbers of researchers (see *The Economist* 2013), cultural models of thinking about science (and life), and the priorities of healthcare systems and societies in general. This often occurs as a result of relying on several more or less interrelated logics that can rarely be narrated in a linear way, and which, in some cases, may even work *against* interests based on profit.[2]

The current general importance given to prevention within public health (e.g., Bell 2010; Timmermann 2011) has established a logic of being at constant risk of numerous diseases, sometimes as early as in the mother's womb (e.g., Lemoyne et al. 2012). One central argument of this article, therefore, is that this general idea is thus enabling and sustaining a more specific theory of prevention for Alzheimer's

[1] The Economist (2013, p. 13) recently published an article on "How science goes wrong," stating that "modern scientists are doing too much trusting and not enough verifying… Last year researchers … found they could reproduce just six of 53 'landmark' studies in cancer research… In 2000–2010 roughly 80,000 patients took part in clinical trials based on research that was later retracted because of mistakes or improprieties."

[2] An example from the domain of Alzheimer's research: The side effects of the traditional antipsychotic medications were the main reason for the marketing of the newer, pricier atypical antipsychotics. The latter, however, have also recently come under attack, because atypical anti-psychotics have "their 'own' adverse effects" (Van Melick 2004). "Ironically," psychiatrists Peter Rabins and Constantine Lyketsos note (2005: 1964; emphasis added), "it was only because pharmaceutical companies were seeking an expansion of approved indications for antipsychotic drug use *in dementia*… that the risks came to widespread attention." In addition, a recent study found that atypical antipsychotics are no more effective than certain older ones (Lieberman et al. 2005).

disease by "dislocating" risk from its initial focus on the brain, onto a "whole body-at-risk" logic. As a result, a major portion of the population is transforming into potential dementia patients. The turn toward prevention further changes dementia care from a field that was once dominated by neurological and psychiatric knowledge, into one that can now be integrated into the domain of general practitioners.

The central argument of this article is that there exist two dominant conceptual changes in the recent history of dementia research which are "embedding" the current importance given to prevention: first, what I have called elsewhere a "cardiovascular logic" (Leibing and Kampf 2013), and second, the renewed interest in the long-known concept of mild cognitive impairment (and now even earlier signs of dementia). A third conceptual change that I will only mention briefly here despite its significance in opening up the concept of dementia to a wider number of possible therapeutic interventions (see Leibing 2009a, b for a more detailed analysis) is the inclusion of non-cognitive symptoms into the core definition of dementia.

By insisting on embeddedness and on multiple argumentative strands for explaining recent changes, I want to challenge some prominent narratives surrounding dementia. Specifically, I seek to address the simplification of the complex syndrome of dementia into singular explanatory pathways—a trend often criticized regarding pharmacological marketing (but also a way of deconstructing dementia found among some social scientists; Leibing 2014).

Around 1993

The aforementioned Swiss authors, like their contemporaries of the 1990s, were rather pessimistic in their evaluation of preventive measures: "In the case of dementia of the Alzheimer type (DAT) …(risk factors) are emerging. However, they are not easily altered…"(p. 446). In a similar vein, Rocca (1994) concludes that "[u]nfortunately, current knowledge about risk factors for AD does not justify the conduct of preventive trials or the introduction of large-scale interventions." In the 1990s, like today, risk factors were thought to be at the origin of pathological brain function leading to cognitive decline. The most important risk factors were and remain to be old age, genetic factors, head trauma, and education. These factors, which can appear in highly varied degrees and combinations, implicate different forms of dementia, of which Alzheimer's disease is the most prevalent, at least since the mid-1970s.

Biomarkers at the beginning of the 1990s were either retrospective or confirmative entities. The microscopic examination of brains from deceased individuals with Alzheimer's disease generally revealed a reduced amount of nerve cells, the presence of beta-amyloid plaques that had built up between nerve cells, and an accumulation of tau tangles that had destroyed part of the cell transport system. Although this pattern can be found in the majority of Alzheimer patients' brains, researchers have long-since known that the correlation between amounts of amyloid plaques, tau tangles, and disease manifestations is not entirely

straightforward. Even in the early twentieth century, some researchers wrote of patients who displayed the typical symptoms of a dementia, but without any accumulation of plaques and tangles in the brain (see Berchtold and Cotman 1998); conversely, Gellerstedt's (1933/1934) detailed study showed that 80 % of individuals over age 65 had the typical plaques and tangles associated with dementia, but without any manifestation of dementia symptoms.[3]

In the 1990s, other biomarkers were investigated in vivo: Brain atrophy or the shrinking of the brain, especially in the hippocampus could be seen through modern brain imaging technologies, and proteins in the cerebral spinal fluid and blood were tested for abnormal concentrations. This procedure was generally undertaken as a means to reinforce the diagnostics—with the primary diagnostic tool being cognitive tests—rather than as a preventive measure. The only predictive biomarkers investigated prior to the onset of Alzheimer's disease (sometimes in combination with an analysis of the cerebral spinal fluid and predominantly within the context of research) were the detection of certain genes; for example, the different alleles of the apolipoprotein E (APOE) of which the e4 allele increases the susceptibility for dementia (Tanzi and Parsson 2000). Biomarkers in the early 1990s were, in short, primarily used for confirming diagnosis and for research. As an example, Arai wrote in 1996 about *diagnostic* markers, not about biomarkers:[4]

> "This review describes recent advances in the development of *diagnostic marker(s)* for AD. They include polymorphism of apolipoprotein E (ApoE) and alpha 1-antichymotrypsin as well as cerebrospinal fluid (CSF) tau and CSF-amyloid beta-protein levels, skin biopsy, and pupil dilatation assay by anti-cholinergic agent. In conclusion, ApoE genotyping should not be used as a sole diagnostic test for AD, and that monitoring of CSF-tau appeared to be most promising and reliable *diagnostic aid*" (p. 65; emphasis added).

The 1990s also yielded exciting advances in treatments as the first medications specifically designed for Alzheimer's arrived on the market. These drugs were developed to increase the level and duration of action of the neurotransmitter acetylcholine (and, more recently also memantine, a NMDA receptor antagonist; see Mount and Downton (2006)). Beginning with Tacrine in 1993—a drug that is no longer recommended due to its serious side effects (especially for liver damage)—four second-generation medications (donepezil, rivastigmine, galantamine, and

[3] In 1940, McMenemey (p. 232, quoted in Berchtold and Cotman 1998, p. 182) wrote: "That the pathological changes in this disease are not specific is generally agreed… Nevertheless, *the presence of abundant plaques and neurofibrillary alterations together with extensive atrophy of the neurons is found only in Alzheimer's disease and senile dementia*" (emphasis added).

[4] As a comparison, Noel-Starr et al. (2013) describe the current landscape of dementia research as tightly linked to *bio*markers, which need to get detected *before* the actual diagnosis of dementia: "The first category was the markers of brain β-amyloid (Aβ) deposition, such as low cerebrospinal fluid (CSF) Aβ42 levels and positive positron emission tomography (PET) imaging results using Aβ ligands. (…) The three major biomarkers in this [second] category included elevated CSF tau levels, decreased ^{18}F-fluorodeoxyglucose (FDG) uptake on PET in the temporoparietal cortex, and disproportionate atrophy on structural magnetic resonance imaging (MRI) in the medial, basal, and lateral temporal lobe as well as medial parietal cortex. These biomarkers were also postulated to be useful for the diagnosis of *mild cognitive impairment (MCI) caused by AD and the prodromal stages of AD*" (p. e97, emphasis added).

memantine) were developed that continue to be prescribed worldwide to patients showing cognitive decline.[5] At the latest by 2005, however, it became clear—at least to those reviewing scientific publications—that these newer medications not only had major side effects, but also exhibited only a moderate effect on cognition for some (but not all) patients (e.g., Harvard Mental Health Letter 2004; National Institute for Clinical Excellence [NICE], 2001, 2005; Royall, 2005; Trinh et al. 2003; see also Leibing 2006, 2009a, b). The reason as to why these medications continue to be prescribed—despite the evidence that "[n]one of these treatment effects are large" (Birks 2005, *Consumer Reports* 2012)—rests in the fact that it remains preferable for families, patients, and doctors to take a chance on achieving slightly better functioning for the individual suffering from Alzheimer's for some time, rather than doing nothing (e.g., Smith et al. 2011): The medications' "success appears to be borne of the significant unmet need," wrote Mount and Downton (2006, p. 784). An additional reason for the continued prescription of these medications is the recent redefinition of what these medications are targeting, which has subsequently led to new positive results in outcome studies (see below).

Around 2013

In 2013, the list of risk factors and biomarkers for Alzheimer's disease are almost identical to those found in parallel publications from around 1993:

The authors of the second study, however, mentioned in the introduction of this article (Carrillo et al. 2013)—the majority of whom are associated with pharmaceutical companies—are more optimistic than their Swiss colleagues were two decades earlier: "There is … increasing evidence suggesting that many risk factors that contribute to the development of late-life dementias are modifiable. … [S]tudies have suggested that education, complexity of occupation, and an engaged lifestyle have protective effects … [U]p to half of AD cases may be attributable to modifiable risk factors…." (p. 123)

The current excitement surrounding *prevention* as a new focus in dementia research is displayed through a number of recent initiatives. At the International Psychogeriatric Association's 2009 conference on "Pathways to Prevention," for example, the organizers noted "there was a sense of being at the beginning of a new era in geriatric psychiatry in which prevention is becoming an increasing focus" (Rapoport and Mulsant 2010). The Alzheimer's Early Detection Alliance (AEDA) was founded by the American Alzheimer's Association and designed to "educate people about the signs of Alzheimer's, the importance of early detection and the resources available to help them" (Alzheimer's Association 2013). In addition, in The European Dementia Prevention Initiative (EDPI), three large cohorts of middle-aged individuals will be followed over a longer period, in an attempt to understand cardiovascular care as preventive or delaying measures of dementia (Dehnel 2013).

[5] Alzheimer medications are also used as so-called smart-drugs in cognitively healthy individuals (see for example Mehlman 2004).

A book written for the general public, *Defying Dementia*, (Levine 2010), further exemplifies this emergent preventive logic. Levine, a neurologist, argues that "accelerated brain aging and neuronal damage" become more accentuated through "diabetes, obesity, hypertension, elevated cholesterol, smoking, excessive alcohol and drugs." In the afterword, Levine summarizes his arguments: "Preventive measures should be thought of as a three-legged stool needing all three legs to hold any weight. The three legs are exercise, cognitive activities, and diet" (pp. 210–211). Two major conceptual changes allow for this new rhetoric of prevention: the importance given to cardiovascular risk factors (see Table 1: "2013"), and the investigation of biomarkers even before the first onset of symptoms.

When looking more closely at the Swiss article from 1993, however, a similar argument can be found: "The well-established *cardiovascular risk factors* such as hypertension, diabetes, and overweight are effective in the etiopathogenesis of vascular dementia. Their treatment by diet and drugs is therefore indicated" (p. 446; emphasis added). Cardiovascular factors, played a role at that time, but only within the carefully distinguished categories of "vascular dementia" and "mixed dementia," both of which were far outnumbered by the dominant diagnostic of "Alzheimer's disease." While this division is still in use, the boundaries between the different categories have become increasingly porous: Many specialists now practically merge these once separated conditions under the name of "dementia" or "Alzheimer's disease" (e.g., Kalaria 2010).

Until the 1960s, dementia in elderly individuals was usually called "arteriosclerotic dementia" (Alzheimer's disease referred to the early-onset dementia). This name, introduced by Otto Binswanger at the end of the nineteenth century, was used to define a condition of cognitive decline secondary to the atherosclerosis of cerebral vessels (Battistin and Cagnin 2010). In 1974, neurologist Vladimir Hachinski criticized this idea for being misleading and proposed instead the term "multi-infarct dementia" (MID); Hachinski thus introduced the notion that cognitive decline needed an accumulation of cerebral infarcts. Alzheimer's disease was seen as a separate disease entity that was a problem of brain chemistry (although Alois Alzheimer had considered the possibility of vascular risk factors). This conceptualization became a dominant idea in dementia research, especially following the highly influential Newcastle study, which, conducted by neurologist Sir Martin Roth and colleagues (e.g., Blessed et al. 1968), demonstrated the correlation between disease manifestation and the amount of amyloid plaques and tau tangles in the brain (and not AVCs). This became a fundamental part of the contemporary understanding of Alzheimer's disease and the foundation of the current research focus on amyloid plaques as central for possible pharmacological interventions.[6]

[6] Since this article refers to a long history in which the concept "Alzheimer's disease" has changed a number of times, a short summary is included here: 1. Alois Alzheimer described in 1906 (Alzheimer 1907) the *early-onset form,* which Kraepelin coined Alzheimer's disease (1910). Parallel to this, there existed the late-onset form, which was generally described as arteriosclerose. 2. Arteriosclerose then became vascular dementia in the 1970s, and infarcts in the brain (small AVCs), together with the "hardening of the arteries" were seen as the etiology. 3. Roth et al. in the late 1960s established the correlation between tau tangles and amyloid plaques as the main biomarkers of AD. 4. Katzman (1976)

Table 1 Based on Rocca (1994) and Van Dujn et al. (1994) and on Alzheimer's Association (2013) and Alzheimer's Disease International (2013)

Alzheimer's disease	1993	2013
Main risk factors	- Family history	- Family history
	- Genetics	- Genetics
	- Age	- Age
	- Education	- Education
	- Head trauma	- Head trauma
	- Down's syndrome	- Down's syndrome
	- Parkinson's disease	- Parkinson's disease
	- Late maternal age	- Social isolation
	- Depression	- Depression
	- Down syndrome	- Down syndrome
	- Aluminum	- Heart-head connection (cardiovascular health—diabetes, hypertension, etc., incl. smoking)
	- Hypothyroidism	
	- Smoking	
	Others	Others
Main biomarkers	- Genes	- Genes
	- Amyloid and tau proteins	- Amyloid and tau proteins
	- Brain atrophy	- Brain atrophy

In fact, while the link between cardiovascular risk factors and Alzheimer's disease has been noted before, only recently have researchers given it specific attention. The APOE (apolipoprotein E) gene, and especially its allele $\varepsilon 4$ (e.g., Slooter et al. 1997; Tanzi and Parsson 2000), which is understood to elevate the risk of developing dementia, is also involved in heart disease: APOE is responsible for the transportation of fat in the body. This causal relationship was initially identified in the 1980s (e.g., Yamamura et al. 1984); however, it was widely ignored until 1993 when neurologist Allen Roses (see Roses 2006) made a significant discovery that linked APOE to the "sporadic" Alzheimer's disease (the most common form where heredity plays less of a role than in the rare "familial" form). Roses continues to investigate a cardiovascular link to dementia: He is now the director of his own biotech company that is currently coordinating an international clinical trial utilizing a specific predictive genetic biomarker called TOMM 40 in combination with an existing Japanese anti-diabetes drug that has been reconceived for Alzheimer's disease prevention (see Ranii 2011). The logic of cardiovascular care

Footnote 6 continued
(and Butler who accepted this when he became the first director of the newly founded NIA, the National Institute of Aging) "unified" early-onset and late-onset dementia as Alzheimer's disease, arguing that both are based on the same pathological pathway, while vascular dementia existed as a less important category parallel to AD. 5. Today, vascular dementia and AD are increasingly overlapping under the name of "Alzheimer's disease" (or dementia), therefore, allowing a cardiovascular logic and prevention based on lifestyle (diet, exercise, etc.) that was previously almost exclusively linked to vascular dementia.

as prevention was reinforced by studies showing that certain groups leading a healthier lifestyle in terms of diet and exercise, such as Amish and Seventh-Day Adventists, also have a lower incidence of dementia (Ornish et al. 1998).

In addition, while recommendations regarding dementia and lifestyle have been suggested in the past (e.g., Friedland 2001, Tanzi and Parson 2000, p. 201), it is only in the last few years that a cardiovascular logic has become more commonplace. In terms of prevention, the brain-based training recommendations of crossword puzzles and memory exercises are partly giving way to new preventive measures based on cardiovascular risk factors: "Regular physical activity, in general, is believed to improve brain function, both by increasing blood flow to the brain and by stimulating the production of hormones and nerve growth factors involved in new nerve cell growth. Exercise also raises levels of 'good' HDL cholesterol" (Rabin 2010).

One possible reason for scientific community's delayed emphasis on cardiovascular risk factors could be attributed to the fact that when Roses established the link, hopes were focused on directly targeting the dysfunctional brain chemistry with the new cholinesterase inhibitors: In 1993, Tacrine arrived on the market, although from the beginning—as was the case for its successor drugs—some critical voices argued that the target of this kind of intervention was too narrow for a complex syndrome like Alzheimer's disease (e.g., Levy 1990).

Even Milder than Mild Cognitive Impairment—Prevention and Prediction

Two new sets of diagnostic criteria, both of which try to capture not only symptomatic Alzheimer's disease (as was the standard until recently), but also early-stage asymptomatic development of supposed pre-dementia, are among the many mechanisms helping to "embed" a preventive logic into scientific reasoning. The "Dubois criteria," which emerged from an international working group (Dubois et al. 2007, 2010), as well as the National Institute on Aging/the Alzheimer's Association's criteria (2011) both divide Alzheimer's disease into three phases: (1) dementia due to Alzheimer's, (2) mild cognitive impairment (MCI), and (3) preclinical (presymptomatic) Alzheimer's (see Visser et al. 2012, Alzheimer's Association 2013).[7]

For many years—at least since the 1960s (e.g., Kral 1962)—the concept of "mild cognitive impairment" (MCI) was loosely attached to dementia, therefore, indicating "a transitional period between normal ageing and the diagnosis of clinically probable very early Alzheimer's Disease" (Petersen 2004). In other words, a certain number of people who initially show rather unspecific and "mild" symptoms of forgetfulness and reasoning might later develop Alzheimer's disease.

[7] The Dubois criteria establish that people who are cognitively normal but have a positive brain amyloid PET scan or an AD-like signature in their cerebrospinal fluid (CSF) would be viewed as being asymptomatic at risk for AD. Asymptomatic people who are known to get AD in the future because they carry a rare autosomal-dominant AD mutation are labeled as having "presymptomatic AD." Further, those who show the typical symptoms of dementia, but not the typical biomarkers, would get a diagnosis of "prodromal AD" (see Fagan and Strobel 2011 for the distinction between these two diagnostic criteria sets).

Who exactly constitutes this subgroup is not well understood, although genetic factors seem to play a certain, but not determining, role (Campbell et al. 2013). This concept, with its well-known limitations of predictive unspecificity (certainly not all individuals with memory problems will suffer from a dementia [e.g., Whitehouse and George 2008]), and the concomitant danger of a pathologization (and pharmaceuticalization) of normal forgetfulness, has now become more tightly linked to the core concept of dementia as a second phase. A third, preclinical phase—even more "preclinical" than MCI—is especially relevant for the discussion of a cardiovascular logic:

> [L]arge cohort studies have implicated multiple health factors that may increase the risk for developing cognitive decline and dementia thought to be caused by AD (…) In particular, *vascular risk factors such as hypertension, hypercholesterolemia, and diabetes* have been associated with an increased risk of dementia (Sperling et al. 2011, p. 282; emphasis added, see also Sperling and Johnson 2012).

This third stage, after Khachaturian (2011), "has […] brought the field to the threshold of a new frontier—the struggle toward primary prevention." A *Globe and Mail* article on the different ways to ensure early detection of Alzheimer's risk declared: "It is also possible that early diagnosis may help patients make lifestyle changes that delay the onset of the disease. Studies suggest that exercise and a healthy diet may be protective. Both measures are widely advocated by doctors to prevent heart disease and stroke" (Mcilroy 2010).

These changes in understanding dementia may also influence an important ethical discussion. For a long time, a heated debate existed about whether early signs of dementia risk—particularly risk discovered through genetic testing—should be revealed to the affected individual and their family. While some argued that results should be made available such that necessary precautions could be undertaken (e.g., the last will and testament, or other legal and emotional acts), others argued that since nothing curative could be done and because the revelation could lead to discriminatory practices (e.g., by insurance companies), social stigma, depression, or even suicide, doing so would only cause distress. This is quite apart from the fact that even for the familial form of Alzheimer's, genetics cannot predict with certainty whether dementia will occur (see Pedersen 2010). With the emergence of a cardiovascular logic regarding dementia, however, concrete preventive measures could now be undertaken. In this context, revealing the vulnerability to individuals early on would mean that they could actively engage in diet and other lifestyle changes: "In any case, the presence of [first] memory complaints offers an important opportunity to review cardiovascular risk factors, and counsel the individual on healthy lifestyle issues including tobacco cessation, regular physical and mentally stimulating activities which together may help deter the onset of dementia," suggest Gauthier et al. (2011).

The idea that a preclinical condition needs to be made concrete and detectable simply in order to exist is exemplified through the extent to which discourse regarding the two new diagnostic criteria centers on biomarkers. For example, Janssen Pharmaceutica, together with GE Healthcare, announced in December 2010

that they were developing a non-invasive assay for detecting "biosignatures" (the beginnings of the formation of the two most important biomarkers, amyloids and tau tangles) to facilitate early diagnosis and intervention (Johnson and Johnson 2010). Early detection in the preclinical phase was also the target of the *professorship for the prevention of dementia and Alzheimer's-related diseases*, financed by Pfizer Pharmaceuticals at Montreal's McGill University (Pfizer 2010). Pfizer announced that, together with the company DiaGenic (2010), it was developing a technology for the identification of blood-based biomarkers for early onset of Alzheimer's disease. If successful, this would certainly mean earlier (and therefore longer) use of the existing dementia drugs, such as Aricept (see AllBusiness 2007), but also a number of other possible interventions.

Pharmacological Interventions: Definitions and Redefinitions

BPSD

When it became increasingly clear that the five available cognitive enhancers only had a limited effect, pharmaceutical companies became interested in widening the definition of dementia, which until this point, had cognitive impairment as the core symptom. They heavily invested in an existing claim made by health professionals that behavioral and psychological symptoms were important, however, had thus far been largely excluded in discourse due to the dominance of "the cognitive paradigm" (cf. Berrios 1990). The official category BPSD (Behavioral and Psychological Symptoms of Dementia), which was the result of a consensus conference in Landsdowne, VA in 1996, and was sponsored by Janssen Pharmaceuticals, had a major impact on research, intervention, and definition of dementia. In terms of interventions, previously existing drugs, like the cognitive enhancers, began to be tested for non-cognitive outcomes such as activities of daily living, behavior, and global outcome (e.g., Tariot et al. 2004). These newer targets of pharmacological interventions were all relatively unspecific, and it was no surprise that as a result, positive outcome studies could now be published. A study by Feldman et al. (2003), for instance, claimed that "Donepezil demonstrated a significantly slower decline than placebo in instrumental and basic *ADLs* [*activities of daily living*] in these patients with moderate to severe AD" (p. 737; emphasis added). Further, the treatment of behavioral and psychological symptoms with psychiatric drugs, which had already been in use as a secondary treatment, now became cutting-edge first-line interventions.

Today, BPSD has faded as a category and this is largely attributable to atypical antipsychotics being strongly promoted for BPSD (see note 2). When these medications came under wider attack for their dangerous side effects and the misleading claim that they were more effective than the older (and cheaper) antipsychotics, BPSD was abandoned relatively rapidly. Another factor influencing the desertion of BPSD is the ineffectuality of joining a variety of different symptoms, each needing a specific kind of intervention, some of which would disappear on their own over time, under the same diagnostic roof (see Leibing 2009a, b). Nevertheless, the widening of a once narrow definition of dementia

continues to exist: Alzheimer's Disease International (ADI n.d.) now defines dementia as "a collective name for progressive degenerative brain syndromes which affect memory, thinking, *behaviour and emotion*."

The existing cognitive enhancers, the development of analogous drugs, and the prescription of psychiatric drugs for cognitive, emotional, and behavioral problems associated with dementia do not represent the only pharmacological interventions. Applby et al. (2013) list a number of existing medications that might become "repurposed" for the new conceptualization of Alzheimer's disease, including: *diabetes-related agents, statins, antihypertensives,* anticancer agents, antimicrobials, antiepileptic drugs, antidepressants, antipsychotics, antiasthma compounds, anti-inflammatory medications, antiparkinsonian medications, Methylene Blue, Nicotine, Trehalose, and Dantrolene. The first three medication groups of this list are directly linked to the new focus on cardiovascular risk factors.

Cardiovascular Risk Factors and Statins

The new prolonged pathway of Alzheimer's disease due to early detection implies that as of mid-life, but also increasingly from a younger age ("Cognitive health begins at conception," cf. Barnett et al. 2013), lifestyle changes are considered a preventative measure for Alzheimer's disease. The current prominence of statins, however—despite having a number of associated warnings (e.g., Wilson 2010, Ferenczi 2010)—illustrates that much of cardiovascular risk is treated through pharmacological interventions rather than lifestyle changes: Statins (cholesterol-lowering medications) are currently the most widely prescribed medication group in the United States. Pfizer's Lipitor alone, patented in 1997, earned the company "around US$130 billion during its 14 years on the market, making it the world's bestselling drug of all time" (*The Lancet* 2011, see Greene 2007). For Alzheimer's disease, the use of statins and other cholesterol-lowering medications, as well as anti-diabetes medications and hypertension drugs, is becoming increasingly important (see Sparks 2010, Applby et al. 2013: Table 2). An enormous market is being added to the already existing one if the cardiovascular logic maintains its explanatory forces.[8] In addition, although among the statins, it is only Crestor from AstraZeneca—a drug that made a profit of $5.1 billion in 2012—which still holds its patent (until 2016), a new class of drugs might soon be entering the market, called PCSK9 inhibitors, lowering the "bad" LDL cholesterol by blocking a protein with the same name (Thomas 2013). If the new guidelines recently developed by the American Heart Association and the American College of Cardiology (see note 8) will become implemented, sales of these new cholesterol-lowering drugs might be lower than expected, since the guidelines do not recommend other drugs than

[8] The American Heart Association and the American College of Cardiology have just released new cardiovascular prevention guidelines, in which statins play a major role: "Cholesterol-lowering statin drugs should now be prescribed to an estimated 33 million Americans without cardiovascular disease who have a 7.5 % or higher risk for a heart attack or stroke within the next 10 years." In 2002, the federal cholesterol guideline recommended that people should only take statins if their 10-year risk level was higher than 20 percent for heart disease (stroke was not mentioned) (see American Heart Association 2013).

statins. However, the current wave of critics against the new guidelines shows that the discussion is not over—for instance its "online calculator" seems to be overestimating cardiovascular risk by 75–150 %, while practically every African-American man over 65 would have to take statins (see Kolata 2013). This intense debate shows once again the importance of a cardiovascular logic for the current understanding of Alzheimer's disease, but also for maintaining existing and conquering new pharmacological markets.

MCI and Beyond: The Amyloid Hypothesis

An additional factor that increases the period of intervention for Alzheimer's disease into mid-life or even earlier is the insistence on mild cognitive impairment and presymptomatic dementia. The central argument for this is that the typical biomarkers are found in individuals long before the onset of first symptoms:

> The current thinking is that well before dementia manifests, protein aggregates trigger a number of cellular changes that lead to irreversible neuronal injury. But the crux of the problem for drug development is that Alzheimer's is diagnosed long after this cellular damage occurs, so clinical trials of new drugs for the disease include only people for whom the underlying pathology is already beyond repair. According to this logic, treatments targeting amyloid protein—which are all at this point experimental, as none have been approved by drug regulators—might not do any good (Moyer 2011, p. 235; see also Roe et al. 2013).

Although researchers have found that individuals *without* an accumulation of the β amyloid protein (which the very-early detection argument focuses on) can also develop Alzheimer's disease (Wirth 2013), and further, a Cochrane study showed that the existing cognitive enhancers do not prevent dementia when given to individuals with mild cognitive impairment (Russ and Morling 2012), cognitive enhancers are still considered an important intervention strategy. George Perry, a neuroscientist at the University of Texas–San Antonio, doubts the claim of early detection. He argues that drugs are being developed based on a flawed basic idea. The example of Lilly's semagacestat, which actually worsened symptoms compared to placebo in large phase 3 trials, illustrates that amyloid may be a response to, rather than a cause of, the disease. Perry asserts, "the amyloid theory was very appealing because it offered a therapeutic venue for intervention." But "if amyloid was the sole cause of the disease, removing it should have had a beneficial effect" (quoted in Mayer 2012, p. 235).

On the other hand, Chételat et al. (2013; emphasis added), an independent research team, make a slightly different statement, which does not disregard the amyloid proteins as an indication of trouble:

> As a whole, *there are evidences for which there is absolutely no doubt on*: some cognitively normal elderly have Aβ deposition in their brain, the prevalence of amyloid-positive cases increases in at-risk populations, *the*

> *prognosis for these individuals (as a group) is worse than for those with no Aβ deposition*, and significant increase in Aβ deposition over time is detectable in cognitively normal elderly. *Other points are more obscure*: the relation between Aβ deposition and AD-related changes (cognition, atrophy, hypometabolism and connectivity) is complex, the sequence and cause-to-effect relationships between the different biomarkers are challenged, and the individual outcome associated with an amyloid-positive scan is still unknown…

While amyloid might not be at the origin of dementia, their accumulation nevertheless indicates trouble for some, but not all, individuals who will eventually develop the syndrome; analysis of amyloids should, therefore, go further than simply denouncing (or deconstructing) this biomarker. The critique should instead be directed toward the simplified models (which then get generalized) and their resulting inadequate interventions, while at the same time acknowledging the possibility that valid insights can emerge from research on amyloids. From this analytical perspective, prevention may be possible, if the studies positing that exercise and diet positively influence the β-amyloid deposition are correct (see Maesako et al. 2012), as it seems to be for cognitive health in general. One of the question then becomes, what role do statins and cognitive enhancers play as preventive measures, when an important subgroup may profit from cost-effective exercise programs and, to a certain extent, from diet.

Conclusion—Complexities and Shortcuts

This very abridged overview of the current struggles surrounding meaningful interventions targeting Alzheimer's disease illustrates the recent profound changes in interpreting risk factors and biomarkers associated with Alzheimer's disease. Further, it illuminates the deep doubts surrounding data gathered from researchers financed by the pharmacological industry, and the need to distinguish that kind of data from research, which acknowledges numerous pathways in the explanation of cognitive decline, including—in some cases—such pathways that have been simplified by argumentative shortcuts (for the marketing of drugs, for instance) and, as a result, invalidated by critical analysts. This argument does by no means excuse the immorality of using people's health for profit-making, but rather acknowledges that simplified (and, therefore, wrong, even dangerous) reasoning might still be based on bits and pieces of valid ideas.

A close examination of recent changes in the conceptualization of dementia reveals that any one single therapeutic strategy seems to slip through the fingers of researchers, as a result of the complexity and multiplicity of pathways implicated in dementia. In fact, I suggest the adoption of the name "Alzheimer's syndrome" in order to constantly remind us that solutions, cure, and care continue to require, and likely always will, a multifaceted approach, and further, that multiple diseases are implied when using this umbrella term:

> In the last two decades, it has become apparent that Alzheimer disease involves changes in many overlapping molecular, cellular, and anatomical pathways. Students of the disease may choose to focus their work on neuropathology, protein folding, substrate-protease biochemistry, synaptic structure and function, signal transduction, cytoskeletal biology, inflammation, oxidative metabolism, neurotransmitter pharmacology, metal ion homeostasis, or behavioral phenotyping in murine models. In short, *Alzheimer research touches upon virtually the entire range of biological inquiry* (Selkoe 2012; emphasis added).

It is clear within this complex picture that many pharmaceutical companies will promote and reinforce those pathways that promise sales for their medications (Sismondo 2008); these tend to be *simple* pathways with a powerful explanatory logic. These argumentative shortcuts and its (im)moral aspects have been well documented by a number of studies (e.g., Applbaum 2009; Petryna 2006). However, pointing out such strategies and critiquing them do not necessarily mean that the whole surrounding logic should be abandoned. For instance, the fact that the correlation between biomarkers and the degree of cognitive impairment is not straightforward—some people function well despite having the typical plaques and tangles in their brains associated with Alzheimer's disease, and vice versa—does not necessarily mean that these biomarkers are mere economic ploys of the pharmaceutical industry. Jonsson (2012), for example, studying the genome of 2,000 individuals, showed that some individuals have a genetic mutation that protects them from an amyloid buildup. None of the individuals with this protective mutation suffered from Alzheimer's disease or cognitive decline in old age—a strong argument in favor of the amyloid hypothesis for some, but not all people, as they age.

In a similar vein, assertions that Alzheimer's disease represents normal, or merely one possible manifestation of aging, seem to undermine those who are suffering from this syndrome. While I agree that there comes a point when illnesses can no longer be distinguished anymore from old age, as Sharon Kaufman (2000) has convincingly argued, Alzheimer's—like cancer whose epidemiology shows an increase with age—is a reality for millions of people around the world, and one that causes deep suffering. It would thus be cruel to accept an argument that dismisses the suffering of so many people as a "myth" (Whitehouse and George 2008).[9] In this sense, social scientists and pharmaceutical concerns share a tendency toward argumentative shortcuts, although they emerge from opposing epistemological positions (see Leibing 2014).

Comparing the preventive doubts of 1993 with the turn toward prevention 20 years later illustrates that new logics emerge and become incorporated into scientific reasoning through multiple claims and theories. The question for researchers is how to critically analyze the existing data by separating shortcuts from valid explanatory pathways. The advantage of using embeddedness as an

[9] Peter Whitehouse and Daniel George's argument is, of course, more sophisticated. It is the general idea of non-existence that gets transmitted through such a choice of words that seems problematic to me. I have discussed this point on several occasions with Peter.

analytical tool rests in its ability to examine several historical strands at the same time, while "shortcuts" might help to critically question certain simplified explanations. Very similar to the complexity found in cancer research, I believe that while there may never be a cure, there can be partial victories over some of dementia's destructive forces.

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