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Editorial

It's Groundhog Day! What Can the History of Science Say About the Crisis in Alzheimer's Disease Research?

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Abstract. For years now, Alzheimer's disease (AD) research has been stuck in a Groundhog-Day scenario: an endless time loop with no breakthrough in sight. Disagreement about the validity of the field's dominant approach, based on the Amyloid Cascade Hypothesis, has led to a seemingly unresolvable trench war between proponents and critics. Our paper evaluates the recent scientific literature on AD from a historical and philosophical perspective. We show that AD research is a classic example of the boundary work at play in a field in crisis: both parties deploy historical and philosophical references to illustrate what counts as good and bad science, as proper scientific method and appropriate scientific conduct. We also show that boundary work has proved unable to point a way out of the deadlock and argue that the science system's tools for establishing scientific quality, such as peer review and the grant system, are unlikely to resolve the crisis. Rather, they consolidate the dominant model's position even more. In conclusion, we suggest that some kind of reverse boundary-work is needed that reopens the discussion on the nature of AD, an issue that has never been settled scientifically. Drawing on historical and philosophical work, we make clear that the definition of AD as a biomedical disease for which a cure can be found has consequences, not only for funding opportunities, but also for patients and their lives. A reconsideration of the desirability of these consequences may lead to different choices with respect to research priorities and patient care.

Keywords: Alzheimer's disease, Amyloid Cascade Hypothesis, boundary work, history and philosophy of science, science system

INTRODUCTION

What do Galileo Galilei, Niels Bohr, and Karl Popper have to do with Alzheimer's disease (AD) research? And why do colorful historical references, such as this one, interlace the AD literature every so often:

> Using that reasoning of Copernicus's time and a bit later that of the Salem witch hunts, once the 'heretic' or 'witch' of amyloid-β (Aβ, the putative cause of AD) is removed or deposition prevented, the 'plague' of AD would be eliminated, and in addition, who knows, the crops might even be saved [1].

When we, two historians of science, first came across such phrases when conducting a literature review on the recent history of AD research, we were immediately fascinated. What were canonical

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figures and metaphors from our area of research doing in otherwise highly technical papers predominantly concerned with peptides, plaques, and neurofibrillary tangles?

In this article, we answer this question and diagnose AD research as a classic example of a phenomenon that historians and philosophers have studied for decades: the boundary-work at play in a field embroiled in a scientific crisis. That AD research is in a crisis will not surprise anyone familiar with the literature: many papers in the field today question the scientific quality and even moral integrity of this literature. It is in this context that references to iconic historical figures and debates pop up most frequently. We will show that AD researchers deploy them to illustrate what counts as good and bad science, as proper scientific method, and as appropriate scientific conduct. This is what boundary-work fundamentally is about.

Through a historical survey of our own, we will argue that this rhetorical use of the history and philosophy of science by and large misses the point. Since the early 2000 s, the AD field has been stuck in what we call a Groundhog-Day scenario: an endless time loop with no apparent breakthrough in sight. Boundary-work has proved unable to point a way out of the crisis; it rather seems to imprison the field even more in its repetitive cycle.

Our historical work also shows that the deadlock is unlikely to be broken by the science system's standard tools for establishing scientific quality. In the AD field, peer review and the grant system have worked to consolidate the position of the dominant biomedical model to the extent that it has become extremely difficult to change course.

We suggest that attempts to escape the loop may benefit from some kind of reverse-boundary work that reopens the discussion on the nature of AD, an issue that has never been settled on scientific grounds. Drawing on the work of historians and philosophers of medicine and science, we make clear that the definition of AD as a biomedical disease for which a cure can be found has consequences, not only for funding opportunities, but also for patients and their lives. A reconsideration of the desirability of these consequences may lead to different choices with respect to research priorities and patient care. In conclusion we urge for a collective effort in the AD field—including researchers, funders, clinicians, and patient-representatives—to take a step back and reflect on alternative ways of moving forward.

A FIELD IN CRISIS

What does it mean to say that AD research finds itself in a crisis? After all, if we judge the field by its size, it seems to be positively flourishing. The search for a cure, which began in the 1980s, involves thousands of investigators and billions of dollars in research funds. In 2021, the AD research budget of the United States National Institutes of Health was $3.1 billion—and this is only the public expenditure of a single nation [2]. Add the substantial efforts by the pharmaceutical industry and one can only conclude that AD research is big business. Yet, despite all the hard work, the field has produced disappointingly few clinical results in the past four decades. Nor have researchers been able to agree on a unified theory of the disease's etiology. The hypotheses that do exist are deeply disputed, and the field's current status quo is customarily described in terms of failure and academic strife.

Consider the following news reports for instance. In 2010, the *New York Times* featured a series on 'The Vanishing Mind', with one of the articles tellingly entitled 'Years Later, No Magic Bullet Against Alzheimer's Disease' [3]. In 2012, *Forbes* published a number of blogs on failed clinical trials for potential AD drugs, with one of the authors boldly declaring that the field's main theoretical framework, the amyloid hypothesis, was "dead" [4, 5]. That same year, the *Wall Street Journal* featured a piece on AD researcher Claude Wischik, whose alternative hypothesis that the protein tau is responsible for the disease was said to be ignored in the field due to academic strong-arming: "Science is politics. And the politics of amyloid won" [6]. In 2015, *Science Friday* quoted a scientist comparing the field's dominant hypothesis to "mob opinion" [7]. And in 2017, *The Atlantic* invoked the infamous image of Monty Python's Black Knight to characterize researchers who still hung on to that hypothesis [8]. As *The Telegraph* aptly summarized it that same year, after yet another failed clinical trial: "Do these public failures mean that scientists have been looking in the wrong place all along? Are we at crisis point for research into Alzheimer's?" [9]. Over the past five years, similar news items have been published every few months.

In the history and philosophy of science, the term crisis has a special meaning. In 1962, the philosopher Thomas Kuhn published his seminal *The Structure of Scientific Revolutions*, in which he offered a historical model for scientific development [10]. Challenging the then prevailing view that science progresses

through the steady accumulation of scientific facts, Kuhn argued that science evolves through episodes of what he called "normal science," during which scientists gather around one dominant explanatory model for a certain phenomenon and work from within this model to solve still outstanding puzzles. From time to time, these episodes, which Kuhn called "paradigms," are interrupted by "revolutionary crises." A crisis sets in when scientists lose their faith in the existing paradigm, because it is unable to explain away a growing number of so-called "anomalies": phenomena which the paradigm cannot account for. Eventually, the crisis is resolved by a paradigm shift, in which a new explanatory model replaces the old one. This only occurs, however, if the majority of the scientific community agrees on the viability of the new paradigm. If not, the old paradigm continues to dominate, even if it keeps on producing new anomalies that intensify the feeling of crisis.

Since 1962, *The Structure of Scientific Revolutions* has become a canonical philosophical work. To this day, it continues to be required reading for many graduate students. Yet it has also been criticized for a number of reasons. The paradigm concept has been notoriously difficult to define precisely. Scholars have remarked that Kuhn's model does not do justice to the reality of scientific practice, because revisions in explanatory models happen more frequently and for different reasons than Kuhn suggested. Also, different explanatory models can often happily exist next to one another, without a field falling into complete disarray. What is particularly relevant for our case is that Kuhn based the notion of paradigms on theory change in the natural sciences, with historical examples showing how certain concepts dominate a field for decades or even centuries and shape which questions can be meaningfully asked within a discipline. This is evidently not the case in AD research, an interdisciplinary field where no theory has ever come to dominate research to such an extent that other questions became meaningless.

Still, in the context of this article, Kuhn's work remains a useful *heuristic* to make sense of the crisis vexing the AD field. One, because Kuhn emphasized that a paradigm, even when in crisis, will not be discarded as long as the scientific community cannot agree on an alternative paradigm—an insight to which we will return towards the end of this article. And two, because those engaged in the debate over the supposed crisis in AD research have repeatedly invoked the paradigm concept themselves to refer to the dominant explanatory model in their field [25, 29, 50, 51]. In 2011, for instance, an article addressing the surging crisis in AD research was even titled 'Anti-Aβ Therapeutics in Alzheimer's Disease: The Need for a Paradigm Shift' [61]. Hence, although Kuhn's work has well-formulated philosophical limitations, its renown and intuitive appeal continue to make it a suitable probing device for our purposes.

THE BIRTH OF A PARADIGM

What 'paradigm' in AD research are we talking about then? The explanatory model at stake is the so-called Amyloid Cascade Hypothesis, that was formulated in 1992 to explain the etiology of the disease. AD is a complex affliction, combining clinical symptoms such as memory loss, language problems, and disorganized thoughts, with the presence of abnormal deposits (called senile plaques) and tangled bundles of fibers (called neurofibrillary tangles) in the brain. It is named after the German psychiatrist and neuropathologist Alois Alzheimer, who first linked this brain pathology to the clinical symptoms in 1907, in a case report about his patient Auguste Deter, who had died fully demented at the age of 55. During autopsy, Alzheimer identified the characteristic plaques and tangles in her brain.

The definition of what AD precisely is, however, has been subject to much debate in the twentieth century. Was it really a disease with a distinct pathology? Did the plaques and tangles cause the symptoms of senile dementia, or were they a by-product of aging that may occur earlier in some people than in others? And was AD only a disease when it manifested itself in relatively young people such as Deter, or was age irrelevant for diagnosis? Pathological research in the 1930s further complicated matters by showing that the plaques and tangles described by AD could also be present in the brains of people without any clinical symptoms [11–14]. Until today, there is no agreement on the exact causal mechanisms of the disease, or even on the question if it is in fact a single disease—a point to which we will return later. No effective cure exists.

This is not for lack of trying. Especially over the past half century, staggering amounts of time, money, and effort have been poured into AD research. In the first half of the twentieth century, the idea had prevailed that the clinical symptoms of the disease could best be combated through a 'psychodynamic' approach: psychiatrists attempted to mitigate the behavioral effects of the condition by targeting

the patients' personality factors, which they hoped could be mobilized to counterbalance the symptoms. Among the treatments used were exercise, group therapy, drugs, and electroconvulsive therapy. The emphasis was on mitigating symptoms, prioritizing care over cure, rather than on research into causal mechanisms. Around 1960, however, on the back of the general post-war expansion of basic science, the conviction grew that AD could only be cured or prevented if biomedical researchers first unraveled the causal biological mechanisms of the disease.

The momentum for this biomedical approach began to increase significantly in the 1970s, after large-scale epidemiological research had strongly suggested that symptoms of senile dementia and the presence of plaques and tangles in the brain upon autopsy were correlated. In 1976, in an editorial in *Archives of Neurology*, the neurologist Robert Katzman categorically asserted that AD resulted from pathological alterations of the brain and should therefore be investigated by biomedical researchers [13]. More and more it was argued that, in an aging society, it would no longer do to mitigate the symptoms of an ever more prevalent disease. Researchers and politicians had to invest in finding a cure, which required investigating the disease's biological mechanisms. In 1977, Katzman and neuropathologist Robert Terry organized a seminal 'Workshop Conference on Alzheimer's Disease' in the United States, that was supported by the country's National Institute on Aging, the National Institute of Mental Health, and the National Institute of Neurological and Communicative Disorders and Stroke. With several others, Katzman also instigated the establishment of the Alzheimer's Association in 1980, which would become one of the principal fundraising catalysts for biomedical research on AD. Whereas US federal funds amounted to less than a million dollar in 1976, they would increase to more than 11 million in 1983 and more than 300 million in 1994 [11]. The budget has only increased since then, to more than 3 billion in 2021.

The first findings that suggested a therapeutic approach to AD emerged from biochemical research in the 1970s. The brains of deceased AD patients appeared to have a significant deficit in choline acetyltransferase, an enzyme involved in the production of acetylcholine. Given the role of this neurotransmitter in memory and learning functions, this observation gave rise to the cholinergic hypothesis, which posited that an acetylcholine deficit was the primary driver of AD. Therapy might therefore consist in treating patients with drugs that inhibited the breakdown of acetylcholine by the enzyme cholinesterase. Clinical trials with cholinesterase inhibitors such as tacrine and donepezil, involving patients suffering from mild forms of AD, did indeed slow down the decline of memory and some behavioral functions. Yet the effect was only moderate, and the drugs had no effect on the progression of the disease. Doubts were also raised by studies that found no reduced levels of choline acetyltransferase in patients with mild symptoms. These findings pointed to a more complicated etiology of AD than the cholinergic hypothesis suggested. In AD therapy, however, cholinesterase inhibitors are to this day the only approved drugs to reduce early cognitive and behavioral symptoms [11, 12, 111, 112].

In the 1980s, more and more research began to focus on the role of Aβ, a protein that was shown to be the main component of the senile plaques in AD patients. *In vitro*, it appeared to be neurotoxic, and this led investigators to hypothesize that Aβ, once aggregated in senile plaques, played a causal role in the formation of the typical neurofibrillary tangles, which in turn would lead to synapse loss, neuronal cell death, and cognitive impairment. In 1992, in a seminal *Science* article, scientists John Hardy and Gerald Higgins expressed this interpretation of the disease's etiology as the Amyloid Cascade Hypothesis [17]. The authors acknowledged that the mechanism by which Aβ induced tangle formation and cell loss was not clear, but that the indirect evidence supporting the hypothesis was strong. Genetic studies showed that in one form of early-onset AD (called familial AD), a genetic disposition was involved. In these patients, mutations in certain genes led to an overproduction of Aβ. Other studies showed that the gene responsible for producing the amyloid-β protein precursor is located on chromosome 21, which would explain why Down patients—who have an extra copy of (part of) chromosome 21—often suffer from dementia in later life. These findings were supported by transgenic mice studies, which confirmed that a number of genetic mutations resulted in an overexpression of Aβ, which in turn might lead to plaque formation and behavioral changes.

The Amyloid Cascade Hypothesis was welcomed with great excitement, convincing many researchers that they were on the right track in unraveling the etiology of AD. It enabled the field to rally around a single explanatory model and work from within this model to further elucidate its causal mechanisms and develop possible cures or prophylactics.

In later years, the model often came to be referred to as a 'paradigm,' even though the Amyloid Cascade Hypothesis was never accepted by all those working in the field and alternative hypotheses started to proliferate from the early 2000s onwards.

SEEDS OF DOUBTS

Indeed, already from the beginning, there were doubts about the validity of the Amyloid Cascade Hypothesis. In *The Lancet* in 1992, for instance, researchers pointed to several weaknesses in the evidence adduced in support of the hypothesis. The genetic factors involved in early-onset AD were unlikely to explain the much more common late-onset, non-hereditary form of the disease that manifests after the age of sixty, called sporadic AD. In addition, the transgenic mice models were argued to have limitations: the precise role of the amyloid-β protein precursor in the onset of AD remained unclear, and the deposition of Aβ was not inevitably associated with the development of neurofibrillary tangles. Added to the well-known fact that senile plaques and neurofibrillary tangles were also found in the cortex of aging people unaffected by the disease, all this suggested that other mechanisms, besides amyloid deposition, might be involved [18]. Other studies in this early period raised similar points, cautioning against too much enthusiasm for a hypothesis that was still insufficiently corroborated [19, 20]. The general consensus appeared to be, however, that these anomalies were just exciting puzzles that AD researchers still had to solve. The Amyloid Cascade Hypothesis gave the field a clear sense of direction and many were confident that their efforts would soon pan out in clinical trials halting or even reversing the progression of AD by combatting the overproduction of Aβ in affected patients.

In 1996, neuropathologist Robert Terry, who had been a leading figure in AD research in the 1980s, was one of the first to fundamentally call the amyloid paradigm into question. Were researchers not too riveted by the hypothesis, he wondered, to the extent that they ignored other possible causal mechanisms, such as synapse loss, in the onset of AD? [21]. The tone of Terry's article was cautious and friendly, and defenders of the hypothesis responded in kind: "It is most stimulating to see an alternative to the idea of a central role of Aβ in the pathogenesis of AD, especially because alternatives give us an opportunity to rethink a hypothesis that many people believe is quite established" [22–24]. This and similar reactions convey the impression of a regular scientific debate between peers who respect each other's diverging viewpoints.

From 1997 onwards, however, criticism of the Aβ hypothesis gathered steam, and the tone of the papers became sharper. While genetic studies supported the hypothesis in the eyes of its proponents, others contended that they did not, because animal models only partially and inconsistently reproduced the pathologies observed in human patients. Another problematic aspect remained that the observed pathology of AD does not correlate perfectly with the disease's established clinical symptoms: at the age of 75, one in four people exhibit some AD pathology without having any cognitive complaints. Several researchers proposed, therefore, that senile plaques are actually an initial protective reaction against yet-unknown processes that are the real cause of the disease. If that were true, any therapies targeting the build-up of Aβ might actually quicken the onset of patients' clinical symptoms rather than alleviate them [25–28].

In this period, the more informal letter to the editor in scientific journals became a frequently used vehicle for debating the Aβ hypothesis. Critics started to complain that the amyloid paradigm was too "simplistic" and that its proponents kept relying on "inherently unsatisfying arguments" [25]. They also pointed out that alternative hypotheses were well represented in the literature and that an approach from multiple perspectives was called for, since AD was probably multifactorial in origin [26]. The argument was not that Aβ played no role, but that it could not be the sole cause.

AN ALL-OUT TURF WAR

Then, in the early 2000s, a group of critics published a flurry of articles renouncing the Aβ hypothesis altogether. Centered around neuroscientists James Joseph, George Perry, and Mark Smith, this group drew on vivid metaphors and a mix of entertaining and disparaging comparisons to frame the amyloid camp as unscientific. In 2000, they fired their opening salvo as a letter to the editor of *The Lancet* under the title 'Amyloid-beta Junkies.' [27]. Their substantive arguments were mostly a repetition of earlier criticisms, but the article's rhetoric was starkly different, portraying amyloid proponents as junkies who had to be weaned off their hypothesis for the benefit of all involved. With this, they set the tone for a new episode in AD research, in which

rhetoric, variously intended to persuade, incriminate, or ridicule, acquired the upper hand in the field's academic debate.

Historical analogies were among the most salient rhetorical devices used in this debate. In 2001, Joseph, Perry, and Smith published 'Copernicus revisited,' their longest and most cited paper criticizing the amyloid hypothesis. Throughout, the authors referred to their opponents as "the Church of Holy Amyloid," comparing themselves to Copernicus challenging the geocentric worldview. Those stuck in the Aβ universe were invited to follow them "into the Age of Light and Reason" [29]. In another article that year, the group compared Aβ research to the historical Salem witch hunts, which had been spurred on by the false hope that identifying the "heretic" or "witch" would help to eliminate the plague and save the crops [1]. Like witch hunters, adherents of the hypothesis seemed to assume that "if large enough conclusions based on weak data are presented often enough, people will believe them." In 2002, in a letter to the editor of *The Lancet*, the authors jeered that testing an anti-Aβ vaccine in a clinical trial "[h]arkens back to the time of leeches and exorcism for the removal of bad humor and spirits to restore function." One might think that "such concepts died with the understanding of homoeostatic balance that defines modern biology," yet we apparently still find ourselves in the Middle Ages: among unscientific thinkers clinging to dogma [30].

In reply to these accusations, neuroscientist Dave Morgan acknowledged that it might be "time for iconoclasm" in the field, but that the comparison with the "totalitarian influence" of an almighty Church was flawed. "The authors need to recognize," he wrote, "that most members of the Church of Holy Amyloid were drawn there voluntarily" [31]. This is "just how science works," another commentator wrote. Adding a Kuhnian gloss, one scientist replied that coaxing scientists away from Aβ would require a convincing alternative paradigm—"an alternative God" [32].

Notably, proponents of the Aβ hypothesis now began to draw on historical analogies, too. In 2006, for instance, John Hardy, one of the originators of the amyloid hypothesis, mobilized the history of science to dismiss his critics. Authors who expressed skepticism of the amyloid hypothesis, he wrote, were unable to "suggest any coherent alternative that explains much of the undisputed data":

> [Their] suggestions resemble 19th century discussions of the existence of *phlogisten* [sic], or the existence of ether to explain the propagation of light in the early 20th century, or the distinction between the mind and the brain in the mid 20th century . . . They border on the mystical and the untestable, and, as ideas, they eventually wither and disappear from scientific discussion [33].

Thus Hardy disqualified amyloid critics as bad scientists—pseudo-scientists, if you will—whose faulty ideas would go down in history as another unfortunate example of backward thinking that held up the scientific field for a while.

Of course, for the opposing camp, it was exactly the other way around: history proved that those going against the grain often turned out to be the true scientific heroes. As the *Wall Street Journal* wrote in a feature about amyloid critic and "outcast among peers" Claude Wischik in 2012:

> History is peppered with examples of scientists who struggled against a prevailing orthodoxy, only to be proved right. In 1854, British doctor John Snow traced a cholera outbreak in London to a contaminated water supply, but his discovery was rejected by other scientists, who believed bad vapors in the air caused the disease. In the 1880s, cholera was finally pegged to bacteria found in contaminated water. In 1982, when two Australian scientists declared that bacteria caused peptic ulcers, conventional wisdom had it that stress and lifestyle were to blame. The scientists won the 2005 Nobel Prize in medicine for their discovery [6].

Likewise, in 2018, Australian AD researcher Ian Clark invoked another famous figure from the history of science to illustrate his position in the field:

> The whole Alzheimer's field in this country is very tied up with amyloid. If you don't believe in amyloid you couldn't get a grant for decades in this country. It's like Galileo trying to get a grant out of the Vatican [34].

This was all very unjust, Clark felt, and a sad example of how scientific thinking can be stunted by a backward scientific community for an indecently long time. As any true Galileo, however, those in defense of veracious scientific thinking would eventually stand the test of time. History, after all, was on their side.

HISTORY AS A BOUNDARY-WORK DEVICE

What are we to make of these recurring historical references in the AD debate? Sociologist Thomas Gieryn characterizes such evocations as 'boundary-work,' a rhetorical strategy scientists use to distinguish their own work as intellectually and morally superior to that of others [35]. The motives for this boundary-work can be diverse: to monopolize a field, to bring down the bulwark of a dominant theory, or to convince politicians or funding agencies to provide financial support. The goal is to demarcate 'real science' from 'non-science,' often conjuring up idealist conceptions of what science is or ought to be, using symbolic formulations and figurative expressions. If successful, boundary-work determines what type of research is considered fundable, publishable, and worthy of further exploration. In practice, boundary work brings forth a surprisingly flexible understanding of what counts as science, as boundaries "tend to vary widely depending upon the specific intellectual or professional activity designated as 'non-science"' and upon the particular goals of those drawing the boundaries [36].

Scientists use a variety of symbolic formulations to characterize an activity as scientific or unscientific. Certainly, the group around Joseph, Perry, and Smith was creative enough in the 2000s to conjure up a whole range of metaphors and analogies [37–43]. But history plays a special role in the boundary-work employed in science. As Kuhn argued in *The Structure of Scientific Revolutions*, history fulfils an important function in maintaining the stability of a scientific paradigm: once a theory has become widely accepted, history tends to be (re)written backwards to present the current paradigm as the logical outcome of past events [10]. Historians call this "the invention of tradition," or Whig history, whereby past events are interpreted as inevitable stepping stones leading up to the present, justifying it as a result. The familiar phrase 'we are standing on the shoulders of giants' is another way of rallying these giants into your camp [44]. Hence, when a paradigm shifts, the history of a scientific field is often rewritten to present the new paradigm as the only logical outcome of past accomplishments.

As Kuhn noted, this rewriting is often encountered in science textbooks, where history functions to initiate students into the paradigm for which that textbook is a pedagogical vehicle [45, 46]. In popular science literature, history often serves the same purpose. In much popular literature about AD, historical figures such as Alois Alzheimer and his patient Auguste D. are foregrounded to present a historically unified and progressive view of the field [106]. What is remarkable about the AD literature, however, is that such rhetorical grandstanding also takes place in highly specialized journals: since 2000, AD researchers have appealed to a wide variety of historical figures and analogies in otherwise very technical scientific papers to portray either their own position as eminently scientific (but sadly unacknowledged by their peers) or the other camp as dismally unscientific (but too ignorant or corrupt to acknowledge this). From this period onward, apparently, researchers of opposing camps have felt the need for more than just substantive arguments to win over their peers; they have resorted to *ad hominem* arguments, disqualifying their opponents as unscientific dogmatists.

As amyloid-critics Stephen Robinson and Glenda Bishop put it in a 2002 article in *Neurobiology of Aging*: "Sir Karl Popper warned that dogma was the greatest barrier to scientific progress. Progress, he argued, could only come from championing bold ideas and subjecting them to severe attempts at refutation; uncritical acceptance of hypotheses leads to stagnation" [47]. In another paper, in which they proposed the alternative hypothesis of Aβ as a bioflocculant, they added: "We share Popper's view of scientific progress and it was in this spirit that we dared to wake the sleeping dogma," in spite of the fact that the amyloid hypothesis "is now accepted by the majority of the field as a statement of fact, which has resulted in the abandonment of critical process. Dissonant results must be wrong and are therefore unpublished" [48].

THE MORALISTIC PURPOSES OF BOUNDARY-WORK

Importantly, for both camps, accusing adversaries of unscientific conduct did not merely entail a philosophical or methodological quibble, but also a moral critique. Most biomedical researchers, proponents as well as opponents of the Aβ hypothesis, agree on one thing: AD is a 'dread disease,' a debilitating affliction that in the 21st century will likely affect a significant part of aging populations worldwide and may disrupt entire societies. Thus, a common rhetorical theme in the AD literature, which Robert Butler, the first director of the National Institute on Aging, referred to as "the health politics of anguish," is the evocation of a

sense of moral urgency to justify more research [11, 105]. For Hardy, in fact, 'dread' justified privileging the amyloid hypothesis in the early 1990s: "[it] was to focus research onto the topics we believed were more likely to yield useful clinical results. It was not intended as an academic exercise, and it should be judged, in the long run, by whether it has facilitated that goal" [49]. Using this same reasoning, Hardy has used 'dread' in his moral condemnation of critics of the hypothesis. As he wrote in 2006: "I am aware of a *schadenfreude* concerning the amyloid-based immunotherapies: a jealous hope that the trials will not be successful. In the face of millions of sick people and their families I regard this guilty pleasure, as irresponsible" [33].

In their turn, critics have maintained that it is precisely the dreadful nature of the disease that should morally induce researchers to abandon the hypothesis. As amyloid-critic Jack de la Torre, who considers AD to be a vascular disorder, put it in 2017: "It is unacceptable, in my judgment, when medical researchers (for whatever reasons) steadfastly hold on to a hypothesis that does not help sick patients in any manner" [50].

Going even further, both camps have implicated that the other side's unscientific point of view can only be explained by ulterior motives. According to Hardy, the "chorus of concern" sung by his critics was a "malcontent's chorus, merely whingeing that their grants go unfunded" [49]. Other amyloid researchers agreed with him, stating that the amyloid paradigm is just normal science. According to neuropathologist Colin Masters "we are all subject to the peer review system" and "[w]e have just as many hurdles to jump in convincing our peers that our approach is correct." Thus, "[t]he 'politics' is really about our peers who are poorly informed or hold non-scientific ideas about how to move the field forward" [34].

To this, critics have retorted that it is actually the amyloid researchers who act improperly. As early as 2001, Joseph et al. hinted at breaches of scientific integrity in their analogy of the Salem witch trials: "In a similar manner to that seen of the medieval Church, the CHA [Church of Holy Amyloid] has possibly suppressed all challenges to its authority, even though a plethora of research casts doubt on the validity of the CHA view" [1]. Ten years later, this accusation was made outright. After the failure of a number of clinical trials attempting to reduce the production of Aβ, Mark Smith and pathologist Rudy Castellani wrote:

> The more the neuroscience community perseveres along these lines in the face of accumulating outcome data to the contrary, the more one is left to wonder whether the hypothesis is too big to fail. [. . .] With so much time, money and, indeed, faith invested in the construct, is a negative outcome simply intolerable for the scientific community and society who depends on it? [51].

The 'too big to fail' metaphor, introduced after the financial crisis of 2008, definitely moved beyond the suggestion that most researchers just mindlessly follow whatever is dominant in a given scientific field. Rather, the critics accused amyloid researchers of knowingly and willingly clinging to a flawed scientific theory to further their own careers, with devastating consequences for society as a whole.

More recently, researchers in the field have made even stronger accusations. In 2017, Jack de la Torre compared the amyloid hypothesis to a sinkhole and claimed that the AD literature was corrupted [50]. Many commentators agreed, accusing "[p]eer reviewers, who protected their own interests by rejecting grants, manuscripts, and other opportunities that propose alternative hypotheses." According to one respondent, Hardy and Selkoe are "criminals" [50]. Other researchers referred to amyloid researchers as a "cabal" that "effectively controlled the ideas funded and published, which start-ups received venture investment and which programs were advanced in biopharmaceutical companies where they consulted" [52]. Elsewhere, the term "amyloid mafia" was used [53, 54]. Judging from such damning qualifications, the AD field has landed in a trench war of opposing camps that are no longer in civilized conversation with one another. And as with most trench wars, they are dug in so deep that any chance of reconciliation seems out of sight.

A DISTINCT SENSE OF GROUNDHOG DAY

One reason for the increasing frustration might be how little seems to change in the AD debate. Overlooking the literature between 1995 and 2020, we were struck by the sheer repetition of arguments and accusations floating around. Even some metaphors and historical analogies became repetitive. At some point, while reading the literature, we found ourselves crying out "It's Groundhog Day!"

Around 2010, for instance, after a substantial number of clinical trials had failed and even successful therapeutic clearance of amyloid plaques in the patients' brain had proved ineffective in halting the disease's progression, the AD literature saw a period of soul searching about the validity of the amyloid hypothesis, even among some of its fervent champions [55]. Articles appeared with titles such as 'Reassessing the Amyloid Cascade Hypothesis,' 'Alzheimer's Disease Amyloid Hypothesis Is at the Crossroads,' and 'Anti-Aβ Therapeutics in Alzheimer's Disease: The Need for a Paradigm Shift.' [56–67]. In the end, however, most amyloid researchers remained undeterred by the unsuccessful trials. They proposed reformulations of the amyloid hypothesis or argued that the disappointing results were due to the therapeutic compounds failing to effectively engage the target, to problems with dosing, or to a wrong choice of trial patients. "Currently it appears that the hypothesis is repeatedly and subjectively used to trump the data with which it conflicts," critics Kevin Mullane and Michael Williams commented on this development in 2013 [68].

On the other side of the aisle, trial failures never failed to reinvigorate opponents of the amyloid hypothesis to come up with the familiar metaphors and historical analogies to echo their point. Mullane and Williams, for instance, recycled the comparison between the amyloid hypothesis and Monty Python's Black Knight, who "suffers from unchecked overconfidence and a staunch refusal ever to give up" [68]. And in 2014, a critical review article opened with a familiar quote from Karl Popper: "Whenever a theory appears to you as the only possible one, take this as a sign that you have neither understood the theory nor the problem which it was intended to solve" [69]. In that same article, scientific giants— Niels Bohr and Joseph Lister, this time—were cited to underscore the crucial importance of an open scientific attitude as a recipe against "dogma."

In 2015, this process started anew. After more clinical trials had failed, a new group of researchers began to question the viability of the amyloid hypothesis, professing that perhaps the moment had arrived to "move away from amyloid beta to move on in Alzheimer research," "to face our fears and reject the amyloid cascade hypothesis" [70–72]. At the same time, just as many proponents of the theory reaffirmed that, while "the amyloid hypothesis is on trial," abandoning it would be "premature" [73].

In 2016, *Nature* published a lead article stating that "the jury is still out" [74]. While George Perry was quoted as saying that "the amyloid hypothesis is dead," the journal itself concluded that the "leading Alzheimer's theory survives drug failure." That same year, Selkoe and Hardy published an article commemorating the 25th birthday of the amyloid hypothesis. While they conceded that multiple hypothesis should be pursued to unravel the mystery of AD, they remained convinced of the scientific superiority of their theory. Eventually, it would surely yield clinical results, because "[s]uccess breeds success" [75].

In 2017, more articles were published under titles such as 'Beyond Amyloid.' They harbor the double sentiment that continues to typify the field: the desire to engage with different theories and hypotheses, coupled to an inability to fully move away from amyloid [76, 77]. Thus, in 2018, *Nature* once again headlined with a piece titled "The Amyloid Hypothesis on Trial," wondering whether it was "time to look beyond amyloid-β as the root cause of the condition." The journal tactfully concluded that the theory is "approaching a crucial juncture," a statement copied almost literally from a number of articles published in the early 2010s [38, 78]. That same year, the lack of progress in finding a cure induced Pfizer to withdraw from the field, and the *New England Journal of Medicine* observed in an editorial that we may be "nearing the end of the amyloid-hypothesis rope" [79]. By then, such rhetoric had become a familiar element in the AD literature: we are at the crossroads, we may have to change direction in the near future, but not just yet. As we write, the impasse is still unresolved. The controversial FDA decision, in June 2021, to approve Biogen's drug aducanumab (that removes amyloid plaques) as a disease-modifying treatment for AD has only sharpened the experts' discord on amyloid. Like earlier compounds targeting amyloid, aducanumab failed to pass phase III clinical trials. Yet after Biogen had submitted a reanalysis of part of the data that suggested cognitive benefit, the FDA in the end granted a license under its 'accelerated approval' pathway, even though its expert advisory committee had voted against it almost unanimously. Critics have reacted with dismay, pointing to the procedure's lack of scientific rigor and saying that, instead of benefiting the patients, aducanumab's approval gives them false hope [80, 81, 107]. According to the newest round of very familiar criticism, the amyloid hypothesis has been exposed as "the emperor's new clothes" [82]. The amyloid "church" and its "acolytes" should finally realize it is time to move on [52].

All this is distinctly reminiscent of the 1993 classic movie *Groundhog Day*, in which weatherman Phil Connors wakes up every morning in Punxsutawney to Sonny & Cher's *I Got You Babe*, dragging himself out of bed to pronounce on national television that it is once again Groundhog Day. The AD research field appears to be stuck in an endless time loop forcing those in it to relive the same day—and discussion—again and again . . . and again.

WHAT THE HISTORY OF SCIENCE *CAN* CONTRIBUTE

Eventually, a new dawn rises for Phil, not through a *deus ex machina*, but through a process of spiritual self-realization, which enables him to look differently at the world. He manages to break the repetitive cycle when he stops his obsessive hunt for more skills, status, or power and starts to listen to and appreciate the perspective of others. Might something similar happen in the AD field? Well, this article definitely aims to contribute to scientists' self-realization of the sheer repetitiveness of the AD debate—which we dare say is a more pertinent use of the history of science than invoking canonical historical figures to prove who is right or wrong. Of course, history cannot predict the future. Who knows, a *deus ex machina* might just turn up tomorrow to save the day. But it takes no clairvoyance to see that right now, the field is stuck. Recognizing that this is not just 'normal science' and that a fresh look at the world is needed, is an important first step to move forward.

In this same vein, we observe that boundary-work is not the answer. Boundary-work is aimed at excluding others, at demarcating boundaries between 'us' and 'them'. It can be very effective in acquiring funds or positioning oneself as a lone martyr, but it goes at the cost of estranging others. In the case of AD, these 'others' are even colleagues one would think should be close allies, since all those involved are working in the same, exceedingly complex and technical field that they alone have the expertise to master. As we have seen, the historical and philosophical analogies and metaphors the opposing camps used to distinguish good science from bad science did succeed in dividing the field but have proved ineffective in providing a solution to its real problems.

If this is not what the history of science can contribute, then what might we learn from looking at the past? Drawing on the work of colleagues, we will shine a historical and philosophical light on two aspects of the AD field: one, the historical instability of AD conceptual foundations as an actual disease, and two, the real-world effects of the dominant disease-definition of AD in terms of creating patient identities and funding opportunities for specific scientific fields. We will argue that these aspects are crucially relevant for AD researchers and others to consider. However, our aim is not to provide policy recommendations or a clear path forward. Rather, we hope that historical reflection can help to create space for debate and thus to eventually break the Groundhog Day pattern.

ALZHEIMER'S SHAKY CONCEPTUAL FOUNDATIONS

First, history can help by highlighting a fact that continues to loom large in the background of the AD debate: the issue of what AD really *is* has never been settled, scientifically speaking. That AD is defined today as a distinct disease—that therefore must have its own distinct disease etiology—is to some extent the result of historical circumstance. As historian Jesse Ballenger has shown, the increase in funding for AD research in the 1980s pivotally depended on this biomedical definition. From the perspective of the long-held alternative view that senile dementia was an inevitable by-product of aging, trying to find a cure made little sense. "We certainly aren't going to cure aging," an exasperated scientist pointed out at a 1969 conference on AD [11].

Thus, as Ballenger points out, to make AD research a viable enterprise, researchers had to convince funders that they were fighting a "dread disease," a major killer, the disease of the century even, that had a clear pathological basis that could eventually be targeted therapeutically. For it was only under this condition that governments would be willing to invest large sums of money in fundamental AD research. In this process, Ballenger notes, cure came to trump care in the discourse of the advocates of the disease [11]. Proponents of the biomedical model played on political apprehension over the issue by pointing to the future demographic disaster of an aging, AD-ridden population and the uncontrollable caregiving costs that would inevitably ensue. Hence, they argued, the government had to act prudently and invest funds now into biomedical research that would locate the cause of AD and develop the drug that would either cure or prevent it. It was time for the government to declare

war on senile dementia, with biomedical research as its most powerful weapon [11].

The war metaphor worked: just as Nixon's 'war on cancer' had jumpstarted fundamental biomedical cancer research in the 1970s, it proved very successful in getting funds allocated to the AD field in the 1980s. The single-disease biomedical model rapidly displaced other hypotheses about the condition without having actually disproved them [55]. This dominant framing of AD, historian Lara Keuck argues, evokes an image of the disease "as a much feared medical condition and simultaneously capitalize[s] on the idea of a window to act (before it is too late)" [83]. The Amyloid Cascade Hypothesis implies that clinical interventions should aim at preventing the build-up of Aβ and thus should preferably subject 'patients' to therapies at a stage that they do not yet display any clinical symptoms—while there is still time to act.

This approach hinges on the disease's etiology being clearly established, yet this is not actually the case. Consequently, as Keuck points out, it is morally questionable to "[assign] a broad range of people the responsibility to take action and adopt preventive or early intervention strategies against developing dementia" [83]. For one thing, it identifies individuals who are presumably healthy otherwise as patients of a dread disease, which radically affects their identities and perspectives. Diagnosis, we teach our first-year medical students, is a 'declarative act': just like when a priest declares the bride and groom to be husband and wife, a disease label alters the patients' reality [84, 85]. It affects how they understand and interact with their bodies, how they interpret their recent experiences, and how they live their lives and make plans for the future [86, 87].

Working with concepts such as preclinical and prodromal AD some AD researchers now even label individuals without symptoms or with only mild cognitive impairment as AD patients. Such a diagnosis is based on biomarkers, for instance the presence of Aβ or tau protein in the cerebrospinal fluid. Even if this is useful from a research point of view, it is questionable from a clinical and ethical one. As philosopher Maartje Schermer and AD researcher Edo Richard point out: "Since there is no treatment available and the predictive value is unclear, it may only create a group of 'patients-in-waiting' who may suffer from anxiety, uncertainty and stigmatization, but will never actually develop dementia" [88, 89]. Additionally, there is the development of subjecting these patients-in-waiting to invasive diagnostic procedures and sometimes risky experimental therapies, thereby blurring the boundaries between research and therapy, and thus subjugating the interests of current patients to those of future ones—or, more cynically, to the careers of AD researchers.

Secondly, history can help to point out that the discord in AD research is highly unlikely to be resolved by relying on the science system's standard tools for establishing scientific quality. Neuropathologist Colin Masters' statement "We are all subject to the peer review system" is meant to imply that the research which gets funded and published is *de facto* the best research available, as it has been evaluated by the field's most eminent experts. But as everyone who has ever submitted a paper to a peer reviewed journal knows: it depends heavily on who is asked to review your paper whether your contribution is recognized as 'scientific' or 'flawed.' [90, 91]. This does not mean the system is corrupted—that a 'mafia' or 'cabal' is at work. It simply means that the reality of scientific practice not always aligns with normative scientific ideals such as those propagated by Karl Popper (or Thomas Kuhn, for that matter).

The history of science is replete with examples of research fields, whether in physics, psychology, or history, that have broken down into subspecialties that hardly communicate with one another [92]. In those fields, it matters greatly who gets 'a seat at the table,' who gets to review that one article submission or decide upon that one funding application. Hence, Selkoe and Hardy were right in an unintended sense when stating that "success breeds success." Scientometric studies confirm the dominance of research on the Amyloid Cascade Hypothesis until the late 2010s, and it has been argued that such dominance creates a tunnel effect [93–95]. Once a field has attained such a position, it is likely to have considerable staying power, because the heavier a particular research line has been invested in, the harder it is to change direction, technically, infrastructurally, and financially. It has literally become 'too big to fail'. Peer review then begins to hinder innovation: it keeps the dominant paradigm in place, simply because it is successful in terms of publications, citations, and grants [96–100]. Even more disturbingly: if the (financial) stakes are high enough, adverse criticism from peers may just be ignored, as the recent approval of aducanumab illustrates. More generally, the pharmaceutical industry's commercial interests may contribute in no small measure to a dominant model's staying power [108].

REVERSE BOUNDARY-WORK

Can anything be done about this, or is this "just how science works"? The answer to this question depends upon one's conception of the governance of science. If the scientific community is envisaged as 'a republic of equals' that thrives best when left alone, perhaps not [101, 102]. But if we consider science to be a social activity that is predominantly funded publicly and has real-world effects, it is reasonable to allow all those who stand to gain or lose from that activity to weigh in. In fact, some kind of reverse boundary-work may be needed, that questions oppositions and boundaries, particularly the dominant biomedical demarcation of AD as a singular disease, with a distinct etiology, for which biomedical science will soon find a cure.

There is no lack of alternatives to the purely biomedical approach in the literature. Authors from various fields have argued that senile dementia cannot be separated from brain aging, as it is entangled with all the internal and external factors, material and immaterial, that affect an individual's life from its beginning. Thus, AD cannot be attributed to a single cause or even to a definable, limited set of causes, and research efforts should therefore be directed at the detection and reduction or exclusion of risk factors, that is at prevention and a healthy lifestyle. In the same vein, it has been argued that AD should much rather be approached as a public health issue and that more funds need to be allocated to social interventions and care for patients [54, 109, 110].

After the outbreak of the AIDS epidemic in the 1980s, AIDS activists famously influenced what kind of research was conducted by scientists, pressuring them to prioritize studies that could make a difference now over studies that might be of a more fundamental nature, but would have little clinical effect in the short run [103]. In the AD field, something similar might be said for studies that prioritize care over cure and investigate how we can alleviate clinical symptoms now, rather than putting all bets on the uncertain and long-term project of understanding the disease's etiology. Such a perspective also entails a critique of AD as a dread disease: patients should not be seen as depersonalized 'living dead' whose bodies are just waiting to follow their minds into oblivion. The focus should be on finding ways to help patients to live the final phases of their lives as humans, not zombies [104].

As historians, it is not our job to pronounce upon alternative views. With our historical analysis, however, we hope to have shown two things. One, that the field's treatment of its dominant model has followed a distinct pattern for over two decades now, which will likely continue to repeat itself as long as the main protagonists in the AD field persist in doubling down on their theoretical positions and research strategies. And two, that the treatment of the Amyloid Cascade Hypothesis as a paradigm, however unwarranted philosophically, has had important real-world consequences. In 2001, an AD researcher replied to the criticisms of Joseph, Perry, and Smith that coaxing scientists away from Aβ would require a convincing alternative paradigm—"an alternative God" [32]. We would venture that this thinking in terms of singular paradigms in AD research is part of the problem rather than the solution, not only because it is historically and philosophically unwarranted, but because it strongly affects how funds are allocated, patient identities defined, and treatment plans decided upon.

Our historical overview will hopefully entice new conversations among those active in AD research about their perceptions of the disease, where priorities should lie, and how they can collectively prevent their field from waking up in Punxsutawney yet another day. We are also convinced that these conversations should be held widely and include many voices. Alternative paradigms may not be as mutually exclusive as Kuhn imagined them to be and can live side by side, but they do reflect different ways of looking at the world. What should our priorities be in dealing with AD? When it comes to distributing resources between prevention, curing and care, we will have to ask ourselves how we value the final phases of human lives. This is, at bottom, not a scientific but a political issue.

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