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COMMENT

Alzheimer Disease research and Aβ*56: The star that never was

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Abstract

Alzheimer's Disease is the most common form of dementia which affects 55 million people worldwide. Not surprisingly, it is a key focus of research involving huge funding. Scientific fraud has inevitably surfaced in this research area. This essay discusses a report of alleged fraud and its implications for the credibility of scientific research.

Keywords: *Dementia, possible fraud, addressing scientific misconduct*

Background

Dementia usually results in an irreversible decline affecting all aspects of cognitive function: memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement, impacting activities of daily living. It currently affects six million people in the US and 55 million globally, and is predicted to increase and affect 150 million people by 2050 [1]. Alzheimer's Disease (AD) is the most common form of dementia accounting for as much as 70% of cases. So it is not surprising that AD is a major focus of research, with the US government alone contributing $3.5 billion in 2022 compared to $277 million for Parkinson's Disease and $444 million for stroke [2]. This body of published research lays the foundation for more research on the subject including trials for new therapies. Naturally, scientific fraud has major implications for policy and treatment.

This article discusses a report of alleged fraud in AD research [3] and its possible implications.

Pathology of Alzheimer's Disease

Named after Alois Alzheimer, a German psychiatrist and neuropathologist, who first described it in 1907 [4], AD has a complex neuropathology, with changes occurring due to the accumulation of two key abnormal proteins: Tubulin associated unit (tau) within the neuron or nerve cell, which gives rise to neurofibrils (filaments within the neuron) becoming tangles [5]; and Amyloid Beta (Aβ) forming plaques (amyloid plaques) outside the neuron. These Amyloid plaques are *insoluble*. But the physiological and pathological function of Aβ are unknown, as is the mechanism by which it causes dementia (see: https://d2vlcm61l7u1fs.cloudfront.net/media/0e9/0e987bd0-9493-4c9f-90e4-f845ea8d115f/phpGR1sUm.png) [6].

In 1911 [7], another psychiatrist and pathologist, Solomon Fuller, found that changes seen in AD were not always associated with symptoms of dementia and they correlated poorly with the onset of AD as well as the number of plaques in the brain. This inconsistency continues to affect the search for an effective treatment of AD.

The Amyloid Cascade hypothesis

In 1992, an 'Amyloid Cascade Hypothesis' proposed that deposits of amyloid β protein (AβP) led to all the changes in the brain associated with AD and this hypothesis has been the basis of hundreds of therapeutic trials for AD, almost all of which failed [8].

Another approach has been to look for *soluble* Aβ oligomers (molecules) suspected of causing memory problems in the absence of any neuronal loss, and long before amyloid plaques appear in the brain [9]. It was such a *soluble* Aβ that researchers from the University of Minnesota (UMN) in the US claimed to have identified [10]. Their "landmark paper", published in 2006 in *Nature*, described work done in the laboratory of a highly respected scientist, Dr Karen Ashe, at UMN. Ashe and her colleague Sylvain Lesné reported on their study using a mouse model for AD. They claimed to have found that memory declined in middle-aged mice because a particular protein, which they named Aβ*56, accumulated outside neurons. They further stated that Aβ*56 impaired memory whether or not plaques were present or neuronal loss had occurred.

Since 2006 when it was published, the Nature paper has been cited by about 2,300 scholarly articles [3].

Doubts about the existence of Aβ*56

The initial reaction to this research [10] was enthusiastic [11]. Prior to the publication of the paper, Ashe presented the findings to an Alzheimer Research Consortium in December 2005, where she asserted: "This is the first time that an agent

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that disrupts memory has been purified from the brain of an AD model."[12]

But soon other laboratories reported that they were unable to replicate these results [3].

The concerns grew as doubts were raised about possible image manipulation in Sylvain Lesne's data in another paper he had co-authored [13,14]. In July 2022, a detailed article in *Science* [3] described the suspicions of a neuroscientist, Matthew Schrag, who concluded that the data which showed Lesné's findings of the Aβ*56 oligomer were an "elaborate mirage". Two independent image analysts, Elizabeth Bik and Jana Christopher, agreed with Schrag's suspicions, calling the images on Western Blot "dubious" [3].

Schrag and Bik went on to identify more than 20 suspect papers in which Lesné was a co-author, 10 of them concerning Aβ*56. Schrag contacted many of the journals where these papers were published. Lesné and his collaborators recently published two corrections — one for a 2012 paper in *The Journal of Neuroscience* [15], the other for a paper in *Brain* [16]. The very existence of Aβ*56 is now doubted, and *Nature* issued a cautionary Editor's note on July 14, 2022 [10].

Causes and consequences

The allegations of image manipulation in the *Nature* article have been under investigation since July 2022, and Lesné's case is under review at UMN. Ashe retains her position as professor of neurology at UMN, and continues to be Director of the N Bud Grossman Center for Memory Research and Care which she founded [17]. She acknowledges that the *Nature* article of which she is a co-author may have contained image manipulation, but asserts that the fabrication/fraud does not affect the validity of her work. She has not acknowledged any liability for misconduct, even though she is Lesné's mentor, senior author of the study, and head of the lab where it was conducted. The allegations of misconduct levied against Lesné's as early as 2013 did not seem to have led her to re-examine the work from her lab [18].

Large amounts of money flow into research. In the US alone, the National Institutes of Health has an annual budget of $45 billion [19] with an addition of about $400 billion totally by private investors including Big Pharma and venture capitalists [20]. The monetary benefits, the academic need for research grants, the "publish or perish" ethos, and the desire for fame and prestige can all contribute to errors as well as increasing the prospect of an investigator taking recourse to reporting misleading data. Data fabrication or falsification creates further problems as other researchers, trusting papers published in respected journals, pursue the same line of inquiry. There has been an exponential rise in retractions of scientific articles [21], but once cited they continue to have an impact on the scientific literature [14].

Some hypotheses, such as the one about Amyloid Cascade [22] become so pervasive — with links to funding and other resources — that they are difficult to oppose, illustrating the underlying pathogenesis, as it were, of scientific fraud. Dramatic claims of scientific discovery gain credibility, attracting grants, private investment and backing from world-class medical institutions despite evidence that the underlying research is flawed or fabricated. The work is published in some of the most admired medical journals in the world, which guide the research agenda.

A losing battle against fraud

How effective are our current methods in acting against scientific fraud?

Journals can issue retractions on papers, but this is often years after the original studies were published. Moreover, they may offer a few details and limited context [23]. It is more than a year since suspicions were raised about the images in the *Nature* article, but the investigation is yet to be completed and there is no time frame given for its completion. On another occasion, *Nature* retracted a paper by a high-profile researcher, issuing an apology stating "research funders, research practitioners, institutions and journals — need to put quality assurance and laboratory professionalism ever higher on our agendas, to ensure that the money entrusted by governments is not squandered, and that citizens' trust in science is not betrayed."[24] Would that all journals — including *Nature* — consistently followed this advice!

Even when papers are retracted, unless the papers which have cited them carry a correction — which is unlikely — they may be cited indirectly. Researchers may not be aware of the paper's status. In one instance, in a case of 25 papers retracted for fraudulent data, those papers were cited hundreds of times and less than half the citations mentioned the papers' retracted status [21].

Pre-publication peer review is meant to ensure a proper scrutiny of scientific papers by independent scientists before publication. But peer reviewers, who perform this critical work without payment, are not equipped to detect fraud [25,26].

Institutions generally fail to provide a full public accounting of what they know about the discredited research. For example, when a star researcher at Harvard was found to have committed research fraud, the university did acknowledge this fact, but did not name the 31 papers with data they deemed fabricated or falsified, nor identify the journals that received notices, and declined to do so when asked [27].

In the US, institutions are required to share a copy of the investigations of misconduct findings with the US Office of Research Integrity but the agency can decline to respond to questions from the public, including whether it investigated the matter [28]. Institutional committees often fend off questions about the full scope of their investigation [29] and

may not conduct independent inquiries. Institutions may fire some junior researchers, but the department heads and chiefs of laboratories usually retain their positions.

How to address scientific misconduct

Elisabeth Bik, who has analysed more than 100,000 papers since 2014 and found apparent image duplication in 4,800, and evidence of other ethical problems in an additional 1,700 [26], makes some suggestions:

- Journals must carry out better quality control, paying image analysts and statistical experts to screen accepted papers before publication.
- Journals need to act much faster when evidence of image manipulation arises.
- We need national and international science integrity organisations that can independently investigate suspected cases of fraud and have some ability to punish the guilty.
- Legitimate criticism of scientific research should receive legal protection. [30,31] Journals should pay data detectives who find fatal errors or misconduct in published papers, similar to how tech companies pay bounties to computer security experts who find bugs in software.[32]
- As it becomes harder to distinguish between fake and real data, science might need to move toward a model based on reproduction, where Ph.D. students earn credits for replicating published studies, while the researchers whose work is reproduced get credit as well."

PubPeer [33] which has served as a post-publication whistleblowing platform website, could become global, with agreed upon standards that apply to all published research. Reporting any suspicious data of a particular laboratory/ institution on such a website would be mandatory. The date and content of this notification would be accessible to the public. Action on the report would need to be completed by the Institution involved in reasonable time and the process detailed on the website.

The need for scientific research is imperative as humanity faces new challenges such as climate change and more pandemics. But scientific research must be worthy of public trust. When error or fraud is noticed it must be dealt with openly and with reasonable speed. Too much is at stake for it to be otherwise.

References

1. Press release. Prevalence of dementia is declining among older Americans; Inequalities reduced but still persist. *Rand.org*. 2022 Nov 7[Cited 2023 Jan 23]. Available from: https://www.rand.org/news/press/2022/11/07.html
2. National Institutes of Health. Report. Estimates of Funding for Various Research, Condition, and Disease Categories (RCDC). 2023 Mar 31[Cited 2023 Sep 30]. Available from: https://report.nih.gov/funding/categorical-spending#/
3. Piller C. Blots on a Field? *Science*. 2022 Jul 22; 377(6604) 358-363. https://doi.org/10.1126/science.add9993
4. Alzheimer A, Stelzmann R, Schnitzlein H, Murtagh F. An English translation of Alzheimer's 1907 paper, "Uber eineeigenartige Erkankung der Hirnrinde". *Clin Anat*. 1995; 8(6):429-31. [German]. https://doi.org/10.1002/ca.980080612
5. Schneider J. Neuropathology of Dementia. *Disorders Continuum (Minneap Minn)*. 2022;28(3):834–851. https://doi.org/10.1212/con.0000000000001137
6. Gouras GK, Olsson TT, Hansson O.β-amyloid Peptides and Amyloid Plaques in *Alzheimer's Disease Neurotherapeutics*. 2015 Jan; 12(1): 3–11. https://doi.org/10.1007/s13311-014-0313-y
7. Fuller S. A study of the miliary plaques found in brains of the aged. *Am J Psychiatry*. 2006 Apr 1. https://doi.org/10.1176/ajp.68.2.147
8. Ricciarelli R, Fedele E. The Amyloid Cascade Hypothesis in Alzheimer's Disease: It's time to change our mind. *Curr Neuropharmacol*. 2017; 15: 926-935. https://doi.org/10.2174/1570159x15666170116143743
9. Habashi M, Vutla S,Tripathi K, Senapati, S, Chauhan PPs, Haviv-Chesner A et al. Early diagnosis and treatment of Alzheimer's disease by targeting toxic soluble Aβ oligomers.| *Proc Natl Acad Sci USA*. 2022 Dec 6; 119(49): e2210766119. https://doi.org/10.1073/pnas.2210766119
10. Lesné S, Koh MT, Kotilinek L, Kayed R, Glabe CG, Yang A, Gallagher M, Ashe KH. A specific amyloid-β protein assembly in the brain impairs memory. *Nature*. 2006 Mar 16; 440 (7082): 352–357. https://doi.org/10.1038/nature04533
11. Aβ Star is born? Memory loss in APP mice blamed on oligomer. *Alzforum.org*. 2006 Mar 17[Cited 2023 Jan 31]. Available from: https://www.alzforum.org/news/research-news/av-star-born-memory-loss-app-mice-blamed-oligomer
12. SfN: Amyloid Oligomers—Not So Elusive, After All? Part 1. *Alzforum.org*. 2005 Dec 6[Cited 2023 Jan 31]. Available from: https://www.alzforum.org/news/conference-coverage/sfn-amyloid-oligomers-not-so-elusive-after-all-part-1
13. Pubpeer.com. Comments of Peer 1 and Actinopolyspora biskrensisa. 2013 Jul [Cited 2023 Jan 31]. Available from: https://pubpeer.com/publications/841806329CBD4CD2593E83C5E369EA
14. Grimes DR. What an Alzheimer's controversy reveals about the pressures of academia. *Atlantic*. 2022 Jul 9[Cited 2023 Jan 31]. Available from: https://www.theatlantic.com/science/archive/2022/07/alzheimers-disease-data-fraud-sylvain-lesne/670995/
15. Erratum: Larson et al. Soluble -Synuclein Is a Novel Modulator of Alzheimer's Disease Pathophysiology. *J Neurosci*. 2022 Jun 15; 42 (24): 4953-4955. https://doi.org/10.1523/JNEUROSCI.0896-22.2022
16. Correction to: Brain amyloid-β oligomers in ageing and Alzheimer's disease. Brain. 2022 Aug 27;145(8):e72-e76. https://doi.org/10.1093/brain/awac143. Erratum for: Brain. 2013 May;136(Pt 5):1383-98.
17. University of Minnesota Medical School. Bio: Karen Ashe MD, PhD. Cited on 2023 Nov 03. Available from: https://med.umn.edu/bio/karen-ashe
18. Rogers MB. Sylvain Lesné, Who Found Aβ*56, Accused of Image Manipulation. *Alzforum.org*. 2022 Jul 22[Cited 2023 Jan 31]. Available from: https://www.alzforum.org/news/community-news/sylvain-lesne-who-found-av56-accused-image-manipulation
19. National Institutes of Health. What we do. Budget. Last reviewed 2023 Aug 1[Cited 2023 Oct 12]. Available from: https://www.nih.gov/about-nih/what-we-do/budget
20. Gajski L. Privatization of Science – A Silent Phenomenon. *Pannoniana*. 2019 Dec[Cited on 2023 Nov 03]; 3(I-II):239-254. Available from: https://hrcak.srce.hr/file/335633
21. Oransky A Retractions are increasing, but not enough. *Nature*. 2022 Aug 2; 608:9. https://doi.org/10.1038/d41586-022-02071-6
22. Hardy JA, Higgins GA. Alzheimer's Disease: The Amyloid Cascade Hypothesis. *Science*. 1992; 256:184-185. https://doi.org/10.1126/science.1566067
23. Retraction challenges. *Nature*. 2014 Oct 1[Cited 2023 Oct 12]; 514:5. Available from: https://www.nature.com/articles/514005a
24. STAP retracted. *Nature*. 2014 Jul 2[Cited 2023 Oct 12]; 511:5-6. Available from: https://www.nature.com/articles/511005b
25. Glonti K, Boutron I, Moher D, Hren D. Journal editors' perspectives on the roles and tasks of peer reviewers in biomedical journals: a qualitative study. *BMJ Open*. 2019;9(11): e033421. Available from: https://doi.org/10.1136%2Fbmjopen-2019-033421
26. Bik E. Science has a nasty photoshopping problem. *New York Times*. 2022 Oct 29[Cited 2023 Jan 31]. Available from: https://www.nytimes.com/interactive/2022/10/29/opinion/science-fraud-image-manipulation-photoshop.html?searchResultPosition=1

27. Taylor M, Heath B. Years after Brigham-Harvard scandal, U.S. pours millions into tainted stem-cell field. *Reuter's*. 2022 Jun 21[Cited 2023 Jan 31]. Available from: https://www.reuters.com/investigates/special-report/health-hearts-stem-cells/
28. Office of Research Integrity, US Dept of Health and Human Services. Frequently Asked Questions. 2016 Aug 4[Cited 2023 Jan 31]. Available from: https://ori.hhs.gov/frequently-asked-questions#4 [See: Answer 18].
29. Baker T. Stanford launches probe into President Tessier-Lavigne's research following 'Daily' investigation on allegations of scientific misconduct. *Stanford Daily*. 2022 Nov 30[Cited 2023 Jan 31]. Available from: https://stanforddaily.com/2022/11/30/stanford-opens-investigation-of-president-tessier-lavigne-following-daily-article-on-allegations-of-scientific-misconduct/
30. Davey M. World expert in scientific misconduct faces legal action for challenging integrity of hydroxychloroquine study. *Guardian*. 2021 May 22[Cited 2023 Jan 31]. Available from: https://www.theguardian.com/science/2021/may/22/world-expert-in-scientific-misconduct-faces-legal-action-for-challenging-integrity-of-hydroxychloroquine-study
31. Besançon L, Samuel A, Sana TG, Rebeaud ME, Guihur A, Robinson-Rechavi M. Open letter: Scientists stand up to protect academic whistleblowers and post-publication peer review. *OSF Preprints*. 2021 May 18. https://doi.org/10.31219/osf.io/2awsv
32. Graco WJ. Data Detectives. *Datasciencecentral.com*. 2020 Oct 2[Cited 2023 Jan 31]. Available from: https://www.datasciencecentral.com/data-detectives/
33. Meet PubPeer 2.0: New version of post-publication peer review site launches today. *Retraction Watch*. 2017 Jun 15[Cited 2023 Jan 31]. Available from: https://retractionwatch.com/2017/06/15/meet-pubpeer-2-0-new-version-post-publication-peer-review-site-launches-today/