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Research report

Transcriptional signatures of brain aging and Alzheimer's disease: What are our rodent models telling us?

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HIGHLIGHTS

- Published brain aging and Alzheimer's disease (AD) transcriptomes are studied.
- Human and rodent brain aging profiles are similar.
- Human AD is highly consistent across studies.
- Transgenic AD mouse models are not similar to one another or to human AD.

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ABSTRACT

Aging is the biggest risk factor for idiopathic Alzheimer's disease (AD). Recently, the National Institutes of Health released AD research recommendations that include: appreciating normal brain aging, expanding data-driven research, using open-access resources, and evaluating experimental reproducibility. Transcriptome data sets for aging and AD in humans and animal models are available in NIH-curated, publically accessible databases. However, little work has been done to test for concordance among those molecular signatures. Here, we test the hypothesis that brain transcriptional profiles from animal models recapitulate those observed in the human condition. Raw transcriptional profile data from twenty-nine studies were analyzed to produce p-values and fold changes for young vs. aged or control vs. AD conditions. Concordance across profiles was assessed at three levels: (1) # of significant genes observed vs. # expected by chance; (2) proportion of significant genes showing directional agreement; (3) correlation among studies for magnitude of effect among significant genes. The highest concordance was found within subjects across brain regions. Normal brain aging was concordant across studies, brain regions, and species, despite profound differences in chronological aging among humans, rats and mice. Human studies of idiopathic AD were concordant across brain structures and studies, but were not concordant with the transcriptional profiles of transgenic AD mouse models. Further, the five transgenic AD mouse models that were assessed were not concordant with one another. These results suggest that normal brain aging is similar in humans and research animals, and that different transgenic AD model mice may reflect selected aspects of AD pathology.

1. Introduction

Idiopathic Alzheimer's disease (AD), already the most prevalent form of age-related dementia, is becoming a proportionally greater risk as other dementia rates decrease due to improved cardio- and neuro-vascular health [1]. Aging is the single most influential risk factor for the development of idiopathic AD and the US Census Bureau projects that 20% of the US population will be ≥65 years of age by 2030, up from just 10% in the year 2000 [2,3]. This disproportionate expansion of the aging population is projected to result in increased AD prevalence. It is estimated that the number of Americans with AD will increase from ~4 million in 2000–7.7 million in 2030 and to almost 15 million by 2050 [4]. Despite clear evidence of the profound influence aging has on susceptibility to AD, little basic research using animal models has focused on this interplay.

Although basic research animals, like humans, show age-related changes in cognition [5–8], most non-human species do not

Abbreviations: AD, Alzheimer's disease; CA, *cornu ammonus* of hippocampus; DG, dentate gyrus; EC, entorhinal cortex; FC, frontal cortex; FDR, false discovery rate; GEO, gene expression omnibus; PFC, prefrontal cortex; TG, transgenic.

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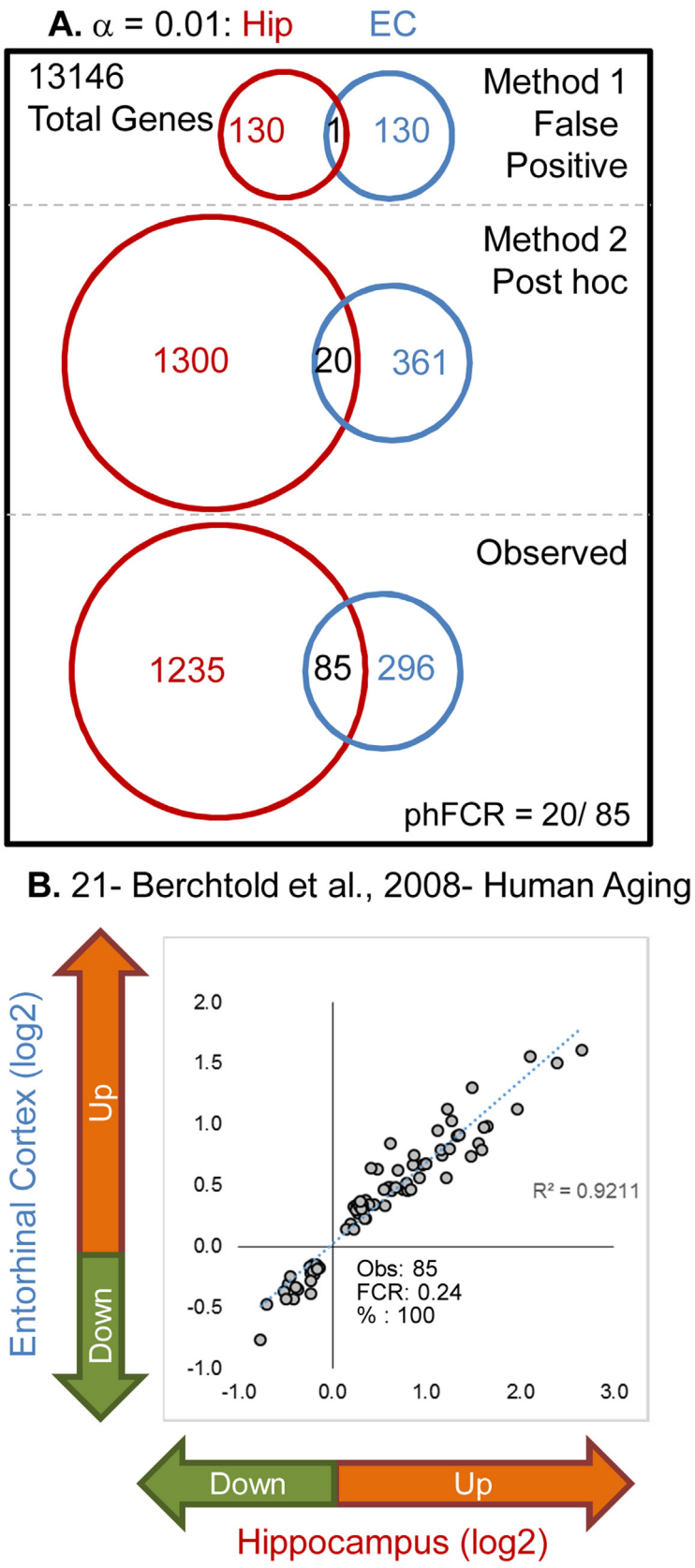

Fig. 1. Assessing similarity/concordance across transcriptional profiles. A. When contrasting studies, method 1 (False Positive) assesses the number of genes expected to be significant due to the error of multiple testing. Total number of genes common to both studies multiplied by the p-value cutoffs used in both studies to identify significant genes (e.g., 13146 total genes * 0.01 for hippocampal (hip) * 0.01 for entorhinal cortex (EC) yields 131 genes expected in each study with 1 gene common between them. Method 2 (post hoc) uses the number of genes observed to be significant in each study, divided by the total number of genes tested, to establish the probability that any gene randomly drawn from the data set would be significant. The number in the overlap is predicted by the product of the post hoc probabilities for each direction in each study. In the Berchtold et al., 2008 hippocampal profile, 358 genes were significantly downregulated and 962 were significantly upregulated. In the same study's entorhinal

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