Higher socioeconomic deprivation is associated with regional vulnerability to atrophy in hippocampal subfields and amygdala in a real-world population with mild cognitive impairment and dementia

Natasha V. Stevanovich [1], Robert Stewart [1,2], Dag Aarsland [1,2], Gayan Perera [1,2], Ashwin V. Venkataraman [1,2]

[1] Centre for Heathy Brain Ageing, IOPPN, King's College London, London, United Kingdom, [2] South London and Maudsley NHS Foundation Trust, London, United Kingdom

Introduction

- 40% of dementia diagnoses may be preventable through the modification of risk factors.
- There is a potential association between socioeconomic status (SES) and dementia prevalence.
- Established dementia risk factors:
  - **Modifiable** (e.g., lifestyle, cognitive reserve, cardiovascular health)
  - **Non-modifiable** (e.g., age, gender, genetic predisposition)
- Socioeconomic deprivation is associated with poorer health outcomes and increased risk of co-morbid diseases that are modifiable risk factors for dementia.
- Deprivation is also associated with reductions in hippocampal and amygdala volume, key regions in neurodegenerative pathology.
- To date, these changes have not been studied in real world populations of cognitive impairment.
- Machine learning approaches have now allowed visualisation of smaller structures such as hippocampal subfields from routine clinical MRIs when previously not possible.

Aim

To investigate the association between socioeconomic deprivation, and **apriori** selected volumes (whole brain, hippocampus, hippocampal subfields, amygdala) in patients with cognitive impairment.

Hypothesis

Less deprived individuals will experience less hippocampal and amygdala atrophy, both overall and within the distinct subfields.

Methods

3,075 patients from SLaM Image Bank (mean age 77, 58% female, 40% minoritized ethnicity, AD (n=2003), MCI (n=660), VaD (n=239), other/unspecified (n=173) were included in this retrospective cohort study.

Inclusion: diagnosis of cognitive impairment or dementia (ICD-10) post MRI scan, >50 years, within SLaM Image Bank.

Exclusion: absence of available MRI scan, total intracranial volume (TIV) data, index of multiple deprivation (IMD) data, TIV <650ml threshold.

Multiple linear regression models adjusted for age, gender, ethnicity, and modifiable risk factors were compared with hippocampal subfields, whole hippocampus and amygdala with stratified analyses for cognitive impairment subtypes.

Measures

Socioeconomic Status (SES)
- London Specific Index of Multiple Deprivation
- Official measure of relative deprivation in England
- Determined by postal codes (Department for Communities and Local Government, 2019)
- Higher scores indicate higher deprivation

Brain Volume

MRI scans from SLaM Image Bank
- Segmented using DeepFLASH and ANTsX Pipelines with DSK atlas applied
  - Regions of Interest (ROIs):
    - Overall Total Intracranial Volume (TIV)
    - Left and right: Hippocampus, Hippocampal subfields (anterolateral entorhinal cortex, CA1, Dentate Gyrus/CA2/CA3/CA4, Parahippocampal Gyrus, Perirhinal Cortex, Posteromedial Entorhinal Cortex, Subiculum) and Amygdala

Dementia Risk

Presence or absence of four well documented MRF's of dementia linked to lower SES
- Hypertension
- Cerebrovascular incident
- Diabetes mellitus
- Asthma

Results

Of our 19 regions of interest, 18 were found to be significant when adjusted for age, gender, ethnicity and modifiable risk factors.

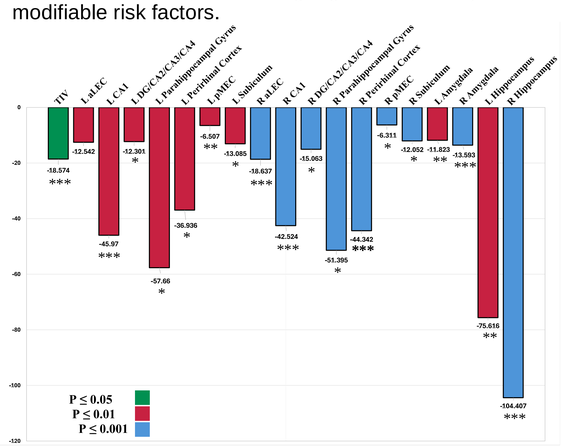

Figure 1. *Bar graph illustrating the decreases in hippocampal and amygdala volume associated with socioeconomic deprivation, as determined by linear regression model. The model was adjusted for age, gender, ethnicity, and modifiable risk factors for dementia (hypertension, diabetes, cerebrovascular accident, and asthma). IMD score was measured in ten-unit increments, where a one-unit change in brain volume represents a ten-unit increase in IMD score.*

Region of Interest (ROI)	Model 3: All Cognitive Impairment Groups	Model 4: MCI	Model 4: Alzheimer's Disease
Total Intracranial Volume	***-18.574	***-26.657	***-19.073
Left aLEC	-12.542	*0.000	-0.008
Left CA1	***-45.970	***-0.002	-0.026
Left DG/CA2/CA3/CA4	*-12.301	**0.003	-0.008
Left Parahippocampal Gyrus	*-57.660	-0.002	-0.036
Left Perirhinal Cortex	*-36.936	-55.072	**-53.824
Left pMEC	**-6.507	*0.000	-0.004
Left Subiculum	*-13.085	**0.005	-0.008
Right aLEC	***-18.637	-0.011	-0.011
Right CA1	***-42.524	-0.002	-0.022
Right DG/CA2/CA3/CA4	*-15.063	*0.000	-0.008
Right Parahippocampal Gyrus	*-51.395	-60.972	*-63.696
Right Perirhinal Cortex	***-44.342	-0.026	*-0.032
Right pMEC	*-6.311	-0.001	-0.004
Right Subiculum	*-12.052	**0.004	-0.007
Left Amygdala	**-11.823	-0.002	-0.007
Right Amygdala	***-13.593	-0.011	-0.007
Left Hippocampus	**-75.616	-0.019	-0.049
Right Hippocampus	***-104.407	-0.020	-0.064

* = P ≤ 0.05
** = P ≤ 0.01
*** = P ≤ 0.001

Figure 2. *Table illustrating the significant decreases in hippocampal and amygdala volume associated with socioeconomic deprivation, as determined by multiple linear regression models. Both models adjusted for age, gender, ethnicity, and modifiable risk factors for dementia (hypertension, diabetes, cerebrovascular accident, and asthma), with Model 4 stratified by cognitive impairment group. IMD score was measured in ten-unit increments, where a one-unit change in brain volume represents a ten-unit increase in IMD score.*

All volumetric output measured in millilitres, ratioed by 1000 and corrected for patient head size divided by total intracranial volume.

Key Findings

We show that higher deprivation is associated with distinct hippocampal subfield and amygdala volume atrophy in cognitively impaired individuals. When stratified, the strongest associations between higher IMD and reduced hippocampal subfield and amygdala volumes were observed in the AD and MCI groups.

Limitations

- Fluctuating SES
- Heterogeneity within dementia subtypes
- IMD score does not specify which SES factor (e.g., education, crime, healthcare access, etc.) could be driving neurodegeneration

Conclusion

- Socioeconomic deprivation may have a larger role in reflecting the regional vulnerability to hippocampal subfield neurodegeneration than previously thought.
- Potential for more deprived individuals to experience greater pathways for elevated dementia risk, earlier dementia onset, accelerated atrophy and rapid progression of clinical symptoms.
- Association likely reflects social and environmental conditions experienced by individuals in lower socioeconomic environments furthering the need for evidence-based interventions.
- Future studies should examine the mechanistic associations between specific factors of SES such as education, crime rates, chronic stress and subfield specific atrophy.

References

- Butterworth, P., Cherbuin, N., Sachdev, P., & Anstey, K. J. (2012). The association between financial hardship and amygdala and hippocampal volumes: Results from the PATH through life project. Social Cognitive and Affective Neuroscience, 7(5), 548–556. https://doi.org/10.1093/scan/nsr027
- Department for Communities and Local Government. (2019). English Indices of Deprivation 2019 FAQs.
- Hunt, J. F. V., Buckingham, W., Kim, A. J., Oh, J., Vogt, N. M., Jonaitis, E. M., Hunt, T. K., Zuelsdorff, M., Powell, R., Norton, D., Rissman, R. A.,
- Asthana, S., Okonkwo, O. C., Johnson, S. C., Kind, A. J. H., & Bendlin, B. B. (2020). Association of Neighborhood-Level Disadvantage with Cerebral and Hippocampal Volume. JAMA Neurology, 77(4), 451–460. https://doi.org/10.1001/jamaneurol.2019.4501
- Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S.G., Dias, A., Fox, N., Gitlin, L. N., Howard, R., Kales, H. C., Kivimäki, M., Larson, E. B., Ogunniyi, A., … Mukadam, N. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. The Lancet, 396(10248), 413–446. https://doi.org/10.1016/S0140673620303676
- Mueller, S. G., Schuff, N., Yaffe, K., Madison, C., Miller, B., & Weiner, M. W. (2010). Hippocampal atrophy patterns in mild cognitive impairment and Alzheimer's disease. Human Brain Mapping, 31(9), 1339–1347. https://doi.org/10.1002/hbm.20934