Interrelationships among self-reported orthostatic hypotension, white matter hyperintensities and hippocampal volume in an 8-year longitudinal study of a young-old cohort

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Areas of interest

Cardiovascular risk factors for cognitive decline, brain ageing, and dementia

• **Postural hypotension or orthostatic hypotension (OH)**
  Definition: orthostatic hypotension as a SBP fall at least 20 mmHg and/or a DBP fall at least 10 mmHg within 3 min of standing. ‘head rush’ ‘dizzy spell’ more common in those with low blood pressure

• **Depressive symptoms**
  Both cardiovascular risk factors, both have also been linked to brain structure and age-related brain changes
Orthostatic hypotension (OH)

- Rapid change in blood pressure leads to rapid change in cerebral blood flow, loss of perfusion.
- Angelousi et al. 2014 Meta-analysis of 28 studies linked OH to coronary disease, heart failure, and arrhythmias. And overall mortality [pooled hazard ratio in random-effects model = 1.36 (1.13–1.63), P < 0.001].
- OH is understudied as a risk factor for dementia and cognitive decline, but has been linked to increased cerebrovascular events and white matter hyperintensities (eg. Colloby et al, BJP, 2011).
Late-life depression –OH, brain atrophy associations

Depression is more prevalent in people with OH

- Cohort study: Irish Longitudinal Ageing Study (TILDA) reported association of symptomatic OH (SOH) and late-life depression (Regan et al, BMC 2013).
- Case-control study: compared 17 depressed and 17 non depressed and found OH more common in depressed (Richardson et al. AJGP 2007).

Depressive symptoms and brain volumes

- Cohort study: WHICAP (n = 630) found increased WMH and reduced brain volume, smaller HC, associated with higher depressive symptoms (Geerlings et al, 2012, JAD).
Hypotheses

• OH is associated with increased WMH, and HC atrophy
• Depression is associated with increased WMH and HC atrophy
• Effects of OH are at least partly moderated by depression

Note: associations = cross-sectional atrophy = longitudinal change
• Random sample from the population of Canberra and Queanbeyan (N = 2551)
• Baseline age-range: 60-64
• Participants assessed every 4 years
• Measures include: socio-demographic, lifestyle, cognition, personality, employment, health, genetic, and more
Normative MRI substudy

- All 60+ subjects eligible
- 2076 (81.5%) willing to participate
- 622 (30.0%) randomly invited for MRI
- 478 (76.8%) scans acquired Wave 1, 407 at Wave 2, 360 at Wave 3

MRI measures used in this study
- Hippocampal manually segmented
- Intracranial volume
- White matter, grey matter, CSF (SPM)
- White matter hyperintensity volume
- All normalised as appropriate
a) Females 

b) Males


Abnormal signal intensities greater than 6 SDs above the mean white matter intensity were classified as WMH. I.e severe WMH
Depression, OH, covariates

- Depressive symptoms measured by the Goldberg scale
- OH assessed at Waves 2 and 3 by the question:
  
  “When getting up suddenly from a lying position, do you experience faintness, dizziness, light-headedness, nausea or blackout?”

- Exclusion criteria: history of stroke, epilepsy, or clinical diagnosis of Dementia.
- Demographics: age, sex, education
- Objective blood pressure measures also taken
Statistical analysis approach

• Generalized linear models for cross-sectional analyses of Wave 2 WMH data
• Multi-level models for analysis of hippocampal volume change over 3 waves (8 years)
• Quadratic terms included in model to account for non-linear change in volumes
• Covariates and OH included as fixed effects
• Models accounted for missing data
Cross-sectional parameter estimates

<table>
<thead>
<tr>
<th>Region</th>
<th>OH W1</th>
<th>Dep W2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$</td>
<td>$\beta$</td>
</tr>
<tr>
<td>Brain stem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontal lobes</td>
<td>0.139**</td>
<td>0.038**</td>
</tr>
<tr>
<td>Temporal lobes</td>
<td>0.009</td>
<td>0.003</td>
</tr>
<tr>
<td>Parietal lobes</td>
<td>0.112*</td>
<td>0.023</td>
</tr>
<tr>
<td>Occipital lobes</td>
<td>0.037</td>
<td>0.039**</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.007</td>
<td>-0.003</td>
</tr>
<tr>
<td>Anterior horn</td>
<td>0.019</td>
<td>0.057</td>
</tr>
<tr>
<td>Posterior horn</td>
<td>0.235</td>
<td>0.265***</td>
</tr>
<tr>
<td>Periventricular</td>
<td>0.019</td>
<td>0.057</td>
</tr>
<tr>
<td>Whole brain</td>
<td>0.043*</td>
<td>0.009**</td>
</tr>
</tbody>
</table>

Generalized linear model adjusted for age, sex, education, smoking, alcohol, blood pressure,
Mean volume of WMH at Wave 1 by Orthostatic hypertension status Wave 2 (mm$^3$)

Adjust for age, sex, smoking, hypertension and years of education.
n for OH = 112, n for no OH = 294
Hippocampus associations

Unadjusted associations among variables at Wave 2

<table>
<thead>
<tr>
<th></th>
<th>WBV</th>
<th>OH</th>
<th>Gender</th>
<th>Educ</th>
<th>Dep</th>
<th>Smoke</th>
<th>Hypert</th>
</tr>
</thead>
<tbody>
<tr>
<td>L HC</td>
<td>.362**</td>
<td>.083</td>
<td>-.239**</td>
<td>.139**</td>
<td>.022</td>
<td>-.019</td>
<td>.015</td>
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<tr>
<td>R HC</td>
<td>.387**</td>
<td>.072</td>
<td>-.309**</td>
<td>.151**</td>
<td>.036</td>
<td>.000</td>
<td>-.001</td>
</tr>
</tbody>
</table>

Hippocampal volumes not associated with OH or depressive symptoms in cross-sectional adjusted analyses
Estimated change in HC volumes (linear mixed models) unadjusted

Change in volume of the left hippocampus over 8-years

Baseline 4-yrs 8-yrs
OH predicting Left Hippocampal volume change over 8 years

OH x time, p = .013; OH x time_sq, p = .012. Non-OH group show no HC atrophy. Note adjusted for age, sex, education, smoking, diabetes, depression wave 1.
Fully adjusted analyses of OH predicting HC volume change

- Time varying depressive symptoms fully attenuated the effect of OH on left hippocampal atrophy

Covariates: Age, sex, years of education, alcohol consumption, smoking history, apoe-4, diabetes, BP meds, and depression medication
Hypotheses and results

- OH is associated with more WMH  Yes
- OH associated with HC volume  No
- OH associated with HC atrophy  Yes, in unadjusted analyses, and with covariates but not when time-varying depression included in model
- Depression is associated with more WMH  Yes
- Depression associated with HC volume  No
- Depression associated with HC atrophy  Yes
- Effects of OH on HC atrophy are moderated by change in depressive symptoms over time
Conclusion

• Both OH and depressive symptoms are vascular risk factors and are associated with WMH
• They also predicted HC atrophy (left only) where the effect of OH was explained by change in depressive symptoms
• Better measures needed to fully evaluated to better understand the independent versus interactive effects of these risk factors
Strengths and limitations

- Longitudinal, normative neuroimaging data, controlled for many covariates, automated WMH data, narrow age-cohort design.
- Limitation of self-report of OH, – difficult for epidemiology to obtain objective measures.
- More waves of data would provide more reliable estimates of growth curves.
- Lack of clinical diagnosis of depression.
General discussion

- General lack of epidemiological data on OH, yet increasing awareness that *variability* in blood pressure influences brain ageing and accumulation of neuropathology
- Strong reasons from cardiovascular literature and depression literature, to investigate OH and low blood pressure, as well as high blood pressure
- Predictors of change may differ from associations observed in cross-sectional studies
- Depression an important cardiovascular risk factor – complex nexus among depression, OH, cardiovascular disease and brain ageing
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