BRAIN COMMUNICATIONS

Cardiac sympathetic denervation and synucleinopathy in Alzheimer's disease with brain Lewy body disease

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Comorbid Lewy body pathology is very common in Alzheimer's disease and may confound clinical trial design, yet there is no *in vivo* test to identify patients with this. Tissue (and/or radioligand imaging) studies have shown cardiac sympathetic denervation in Parkinson's disease and dementia with Lewy bodies, but this has not been explored in Alzheimer's subjects with Lewy bodies not meeting dementia with Lewy bodies clinicopathological criteria. To determine if Alzheimer's disease with Lewy bodies subjects show sympathetic cardiac denervation, we analysed epicardial and myocardial tissue from autopsy-confirmed cases using tyrosine hydroxylase and neurofilament immunostaining. Comparison of tyrosine hydroxylase fibre density in 19 subjects with Alzheimer's disease/dementia with Lewy bodies, 20 Alzheimer's disease with Lewy bodies, 12 Alzheimer's disease subjects without Lewy body disease, 19 Parkinson's disease, 30 incidental Lewy body disease and 22 cognitively normal without Alzheimer's disease or Lewy body disease indicated a significant group difference ($P < 0.01$; Kruskal–Wallis analysis of variance) and subsequent pair-wise Mann–Whitney U tests showed that Parkinson's disease ($P < 0.05$) and Alzheimer's disease/dementia with Lewy bodies ($P < 0.01$) subjects, but not Alzheimer's disease with Lewy bodies subjects, had significantly reduced tyrosine hydroxylase fibre density as compared with cognitively normal. Both Parkinson's disease and Alzheimer's disease/dementia with Lewy bodies subjects also showed significant epicardial losses of neurofilament protein-immunoreactive nerve fibre densities within the fibre bundles as compared with cognitively normal subjects ($P < 0.01$) and both groups showed high pathologic alpha-synuclein densities ($P < 0.0001$). Cardiac alpha-synuclein densities correlated significantly with brain alpha-synuclein ($P < 0.001$), while cardiac tyrosine hydroxylase and neurofilament immunoreactive nerve fibre densities were negatively correlated with the densities of both brain and cardiac alpha-synuclein, as well as Unified Parkinson's Disease Rating Scale scores ($P < 0.05$). The clear separation of Alzheimer's disease/dementia with Lewy bodies subjects from Alzheimer's disease and cognitively normal, based on cardiac tyrosine hydroxylase fibre density, is the first report of a statistically significant difference between these groups. Our data do not show significant sympathetic cardiac denervation in Alzheimer's disease with Lewy bodies, but strongly confirm that cardiac nuclear imaging with a noradrenergic radioligand is worthy of further study as a potential means to separate Alzheimer's disease from Alzheimer's disease/dementia with Lewy bodies during life.

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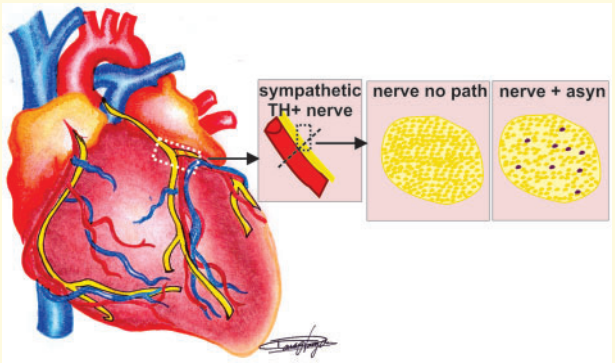
Abbreviations: **DLB** = dementia with Lewy bodies; **AD** = Alzheimer's disease; **LB** = Lewy body; **a-syn**alpha-synuclein; **ADLB** = Alzheimer's disease with Lewy bodies; **PD** = Parkinson's disease; **UPDRS** = Unified Parkinson's Disease Rating Scale; **CN** =non-demented movement control; **ILBD** = incidental Lewy bodies; **SCOPA-Aut** = SCales for Outcomes in Parkinson's disease questionnaire autonomic; **SD** = standard deviation; **M** = male; **F** = female; **PMI** = post-mortem interval; **TH** = tyrosine hydroxylase; **NF** = neurofilament; **Sum** = Summation; **DaTscan** = dopamine transporter single positron emission tomography; **^{123}I-MIBG** = ^{123}I-metaiodobenzylguanidine

Graphical Abstract



Introduction

The Dementia with Lewy Bodies (DLB) Consortium consensus clinical diagnostic criteria have high specificity (Jolly-Tornetta and Wolf, 2000) for diagnosis of patients with the fully developed clinical syndrome, but low sensitivity (McKeith *et al.*, 1996, 2017; Litvan *et al.*, 1998; Nelson *et al.*, 2010; Huang and Halliday, 2013; Malek-Ahmadi *et al.*, 2019). Even in specialist research settings, only 10–30% of subjects neuropathologically confirmed as DLB are diagnosed during life, with the most common misdiagnosis being Alzheimer's disease (Alzheimer's disease). Furthermore, comorbid Lewy body (LB) disease is very common in Alzheimer's disease (Dickson *et al.*, 1991); up to 60% of Alzheimer's disease subjects also have pathologic alpha-synuclein (a-syn) at autopsy (Hamilton, 2000; Tsuang *et al.*, 2006; Uchikado *et al.*, 2006). Some of these are subjects that meet clinicopathological criteria for both diagnoses, Alzheimer's disease and DLB, but most have a-syn that does not meet density and distribution criteria for DLB and hence have been termed Alzheimer's disease with Lewy bodies (ADLB) (McKeith *et al.*, 2005, 2017; Beach *et al.*, 2009). This is a critical concern for Alzheimer's disease clinical trials, as subjects with both Alzheimer's disease and a-syn may have a different clinical course (Malek-Ahmadi *et al.*, 2019) and may not respond well to therapeutic agents targeting only Alzheimer's disease pathology. In the USA, sympathetic neuroimaging is rarely used for the diagnosis of autonomic or movement disorders, but this has been commonly used in Europe and Japan. Tissue studies have shown cardiac sympathetic denervation in both clinical and neuropathologically diagnosed Parkinson's disease (PD) and DLB, but this has not been explored in ADLB (Yoshita *et al.*, 1997, 2001, 2015; Yoshita, 1998; Goldstein, 2001; Orimo *et al.*, 2002, 2008; Fujishiro *et al.*, 2008; Goldstein *et al.*, 2009; Takahashi *et al.*, 2015; Manabe *et al.*, 2017). In this study, we tested the hypothesis that ADLB will be distinguishable from Alzheimer's disease without LB by having lower densities of cardiac noradrenergic nerve fibres.

Materials and methods

Human subjects

Human hearts came from subjects who were volunteers in the Arizona Study of Aging and Neurodegenerative Disorders, a longitudinal clinicopathological study of normal aging, cognition and movement in the elderly since 1996 in Sun City, Arizona (Beach *et al.*, 2008a, 2015). Autopsies were performed by the Banner Sun Health Research Institute's Brain and Body Donation Program (www.brainandbodydonationprogram.org). All subjects signed Institutional Review Board-approved informed consents allowing both clinical assessments during life

Table 1 Patient demographics

DX (*n*)	Age (SD)	Gender (M:F)	UPDRS OFF (SD)	Hoehn and Yahr (SD)	SCOPA-Aut total (SD)	PMI (SD)	a-syn sum Brain (SD)
CN (22)	82 (14)	13:9	6.1 (5.5)	0.2 (0.8)	19.8 (15.7)	6.0 (14.8)	0
PD (19)	81 (6)	16:3	39.4 (18.8)*	2.9 (1.5)*	25.1 (8.5)	3.4 (1.3)	27.2 (5.9)*
AD/DLB (19)	82 (8)	12:7	34.9 (18.6)*	1.8 (1.8)*	27.5 (12.9)	3.6 (1.5)	32.8 (5.6)*
ADLB (20)	80 (8)	13:7	23.9 (23.1)*	1.5 (2.2)	29.3 (10.5)	4.4 (5.9)	13.7 (6.3)*
AD (12)	77 (9)	8:4	17.5 (20.9)	0.6 (1.5)	15.3 (6.0)	3.7 (0.8)	0
ILBD (30)	86 (9)	18:12	8.2 (6.3)	0.0 (0.0)	17.7 (9.8)	4.6 (4.4)	8.0 (8.0)*

AD = Alzheimer's disease; AD/DLB = Alzheimer's disease and dementia with Lewy bodies; ADLB = Alzheimer's disease with Lewy bodies; CN = non-demented movement control; F = female; ILBD = incidental Lewy bodies; M = male; Parkinson's disease = Parkinson's disease; PMI = post-mortem interval; SCOPA-Aut = SCales for Outcomes in Parkinson's disease questionnaire autonomic; SD = standard deviation; UPDRS = Unified Parkinson's Disease Rating Scale.
*$P < 0.05$ post-test when compared with CN (CN).

and several options for brain and/or bodily organ donation after death. All subjects were clinically characterized by expert clinicians and most of them had annual standardized test batteries consisting of general neurological, cognitive and movement disorders components, including the Unified Parkinson's Disease Rating Scale (UPDRS), Hoehn and Yahr staging and the Scales for Outcomes in Parkinson's disease questionnaire autonomic (Damian *et al.*, 2012). Subjects for the current study had a complete pathological evaluation by medically licensed pathologists (Table 1; $N = 121$) and were chosen by searching the Banner Sun Health Research Institute's Brain and Body Donation Program database for cases with a whole-body autopsy and specific clinicopathological diagnoses including controls who were defined as non-demented individuals without parkinsonism and without LB pathology in the brain or examined peripheral tissue (CN, $n = 22$) and non-demented, non-Parkinsonian individuals without any neurodegenerative disorder diagnosis who also had incidental Lewy bodies (ILBD) at autopsy ($n = 30$), Parkinson's disease ($n = 19$), Alzheimer's disease ($n = 12$), AD/DLB ($n = 19$) and ADLB ($n = 19$).

Pathological examination

Complete gross and microscopic pathological examination was performed using standard Arizona Study of Aging and Neurodegenerative Disorders methods and included pathologist assessment of both brain and peripheral organs (Beach *et al.*, 2008a, 2015). Cardiac samples included epicardial and adjacent myocardial tissue collected at the left circumflex coronary artery, lateral to the pulmonary trunk and inferior to the auricle of the left atrium. Tissue blocks were fixed in neutral-buffered formalin and embedded in paraffin. All sections were stained with haematoxylin and eosin for general pathological assessment. Immunohistochemical staining was used to document the presence of a-syn pathology in brain and cardiac nerve fibres. The antibody used for *p*-synuclein (raised against alpha-synuclein phosphorylated at serine 129) was privately developed and its characterization has been previously described (Fujiwara *et al.*, 2002; Walker *et al.*, 2013). The signal development steps have been described in previous publications (Beach *et al.*, 2008b). Tyrosine hydroxylase (TH; Sigma Catalogue # T2928) and neurofilament (NF; ABCAM Catalogue # AB8135) antibodies were used to localize noradrenergic sympathetic nerve terminals and all nerve fibres, respectively. Immunohistochemical procedures were identical for all three methods, except for differing epitope exposure: 20 min proteinase K pre-treatment for *p*-synuclein; 20 min in boiling citrate buffer for TH and no antigen retrieval step for NF. Primary antibody concentrations were 1:10 000 for *p*-synuclein and 1:3000 for TH and NF. Stained epicardial nerve bundles were semi-quantitatively analysed blinded to the final clinicopathological diagnoses. We counted the numbers of NF-positive bundles to ensure a good sample size and sections were blindly graded for TH, NF and *p*-synuclein using templates analogous to those recommended by CERAD (Mirra *et al.*, 1991) with separate semi-quantitative density estimates of either absent (0), sparse (1), moderate (2) or numerous (3) densities within nerve bundles. The neuropathological examination was performed in a standardized manner and consisted of gross and microscopic observations, the latter including assessment of frontal, parietal, temporal and occipital lobes, all major diencephalic nuclei and major subdivisions of the brainstem, cerebellum and spinal cord. Following fresh brain slicing and subsequent fixation in cold 10% neutral-buffered formalin for 36–60 h, histological preparations included paraffin-embedded 6 µm sections, as well as large-format (3 × 5 cm), 40–80 µm-thick, cryoprotected frozen sections. Both sets were stained with haematoxylin and eosin and the former set was also immunohistochemically stained for phosphorylated *p*-synuclein in 10 standard brain regions including olfactory bulb, anterior medulla, anterior and mid-pons, midbrain with substantia nigra, amygdala, anterior cingulate gyrus and three neocortical regions (middle frontal gyrus, middle temporal gyrus, inferior parietal lobule). Each region was graded as 0–4 for *p*-synuclein density using the template provided by McKeith *et al.* (2005). A summary brain score of all 10 regions is recorded to give an overall brain load estimate, with the highest possible score being 40. Senile plaques, neurofibrillary changes and other neuronal and glial

tauopathies were assessed using thioflavin S, Gallyas and Campbell-Switzer methods and were graded blindly as recommended by CERAD with separate semi-quantitative density estimates of none, sparse, moderate or frequent. All scores were converted to a 0–3 scale for statistical purposes. Regions scored included cortical grey matter from frontal (F), temporal (T), parietal (P), hippocampal CA1 (H) and entorhinal (E) regions, with the sum of all brain regions giving a maximum score of 15.

Statistical analysis

One-way ANOVA was used to analyse group differences in demographics; the Kruskal–Wallis test with subsequent pair-wise Mann–Whitney *U* tests were used to analyse group differences in brain and heart a-syn and TH density. Spearman's correlation was used to test for relationships between TH fibre density and a-syn, in both brain and heart.

Data availability

The authors confirm that the data supporting the findings of this study are available at the Banner Sun Health Research Institute's Brain and Body Donation Program (https://www.brainandbodydonationregistration.org) and upon request to the corresponding author.

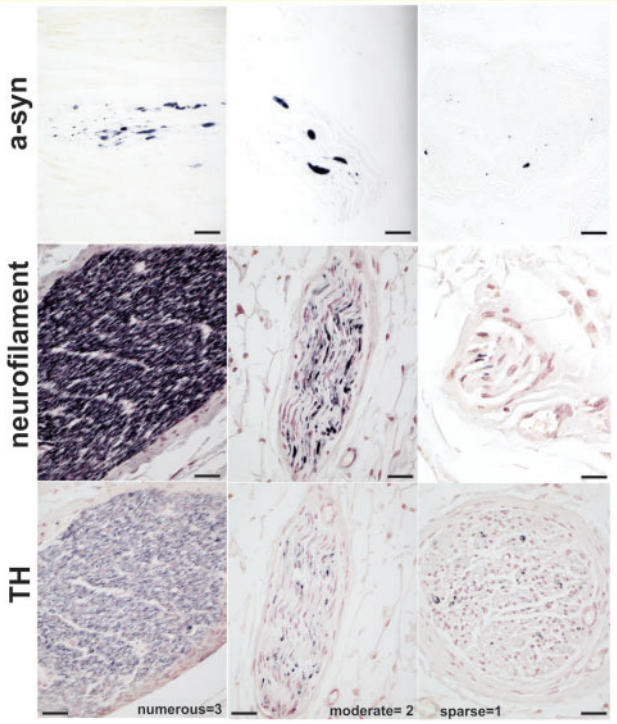


Figure 1 Myocardial immunostaining with *p*-αsynuclein, NF and TH. Numerous, moderate, sparse or absent densities scores were used to analyse nerve denervation and a-syn pathology in autopsy collected myocardia.

Results

There were no significant differences in group mean age or post-mortem intervals (Supplementary Table 1). UPDRS scores were significantly higher in Parkinson's disease, AD/DLB and ADLB when compared with CN, while Hoehn and Yahr scores were only significantly higher in Parkinson's disease and AD/DLB. Furthermore, SCOPA-Aut total scores were significantly different between the groups, but neither neurodegenerative group was significantly different when compared with CN (Table 1). NF staining confirmed the presence of numerous nerve fibre bundles in the epicardium around coronary artery branches in the cardiac tissue blocks (Fig. 1), with an average of 85 nerve fibre bundles per sample. Both Parkinson's disease and AD/DLB subjects showed significant losses of NF protein-immunoreactive nerve fibres within bundles as compared with CN ($P < 0.01$) and both groups showed higher a-syn densities within bundles when compared with CN (Fig. 2; $P < 0.0001$). Cardiac a-syn was also present in ILBD and ADLB, but the mean from each group was not significantly different than CN. Cardiac a-syn densities correlated significantly with medulla, amygdala and brain summation a-syn densities, with medulla showing the strongest correlation (Table 2; $P < 0.001$). Furthermore, cardiac TH-immunoreactive nerve fibre densities were significantly different between the groups ($P < 0.01$), and subsequent pair-wise analysis showed that Parkinson's disease and AD/DLB subjects had significantly reduced TH fibre densities when compared with CN ($P < 0.01$) and Alzheimer's disease ($P < 0.05$). Neither NF nor TH fibre densities in Alzheimer's disease, ADLB or ILBD were significantly different from those of CN. Cardiac TH- and NF-immunoreactive nerve fibre densities were negatively correlated with the densities of both brain and cardiac a-syn, as well as UPDRS scores (Gau *et al.*, 2002).

Discussion

This study strengthens the rationale that sympathetic cardiac denervation might be driven by a-syn pathology, such that an in vivo test for such denervation would allow clinical differentiation between pure Alzheimer's disease and AD/DLB while patients are still alive. While we found no evidence that cardiac denervation could be used to distinguish between Alzheimer's disease and those Alzheimer's disease patients that have a-syn pathology that does not meet DLB criteria, being able to separate cases of AD/DLB from Alzheimer's disease during life would be a huge advance for dementia epidemiologic and treatment studies (McKeith *et al.*, 1996, 2017; Litvan *et al.*, 1998; Nelson *et al.*, 2010; Huang and Halliday, 2013). For instance, close to 50% of the AD/DLB cases used, in this study, were clinically diagnosed during life

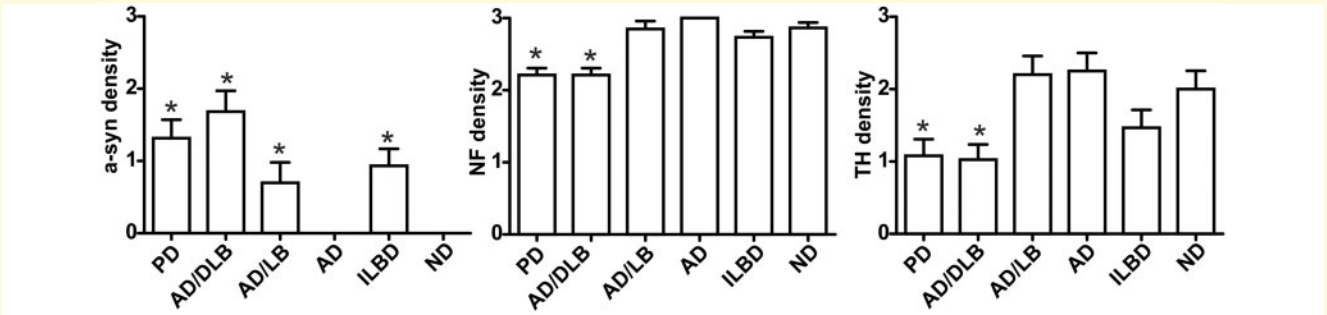


Figure 2 Densities of myocardial nerve immunostained fibres for *p*-αsynuclein, NF and TH. Both Parkinson's disease and AD/DLB subjects showed high a-syn densities in myocardial nerve bundles and significant losses of NF and TH protein-immunoreactive nerve fibres as compared with CN ($P < 0.01$).

Table 2 Statistical correlation of heart pathology with brain pathology and UPDRS score

Correlation	Correlation coefficient	*P*-value
a-syn heart versus a-syn sum brain	0.588	<0.0001
a-syn heart versus a-syn medulla	0.694	<0.000001
a-syn heart versus a-syn amygdala	0.420	<0.000001
a-syn heart versus TH heart	−0.201	<0.05
a-syn sum brain versus TH heart	−0.279	<0.01
a-syn medulla versus TH heart	−0.0323	<0.001
a-syn amygdala versus TH heart	−0.155	NS
a-syn heart versus NF heart	−0.331	<0.0001
a-syn sum brain versus NF heart	−0.547	<0.0001
a-syn sum medulla versus NF heart	−0.612	<0.000001
a-syn sum amygdala versus NF heart	−0.445	<0.000001
UPDRS versus a-syn heart	0.284	<0.001
UPDRS versus TH heart	−0.178	0.08
UPDRS versus NF heart	−0.430	<0.0001

a-syn = pathologic alpha-synuclein; NF = neurofilament; sum = summation; TH = tyrosine hydroxylase; UPDRS = Unified Parkinson's Disease Rating Scale.

as Alzheimer's disease alone. The symptoms of these subjects did not manifest like typical DLB and may have a different clinical course (Malek-Ahmadi *et al.*, 2019). Furthermore, it is also known that up to 60% of Alzheimer's disease subjects have comorbid a-syn at autopsy (Hamilton, 2000; Uchikado *et al.*, 2006; Malek-Ahmadi *et al.*, 2019). Some of these subjects received a final autopsy diagnosis of Alzheimer's disease and DLB, while others had a-syn that did not meet density and distribution criteria for DLB. This is a critical concern for Alzheimer's disease clinical trials, since subjects with both Alzheimer's disease and a-syn may be less responsive or even resistant to Alzheimer's disease-specific therapeutic agents. Those DLB subjects who do not have at least two core clinical features (cognitive fluctuations, Parkinsonism, dream enactment behaviour and visual hallucinations) are more likely to be misdiagnosed as Alzheimer's disease or dementia NOS (McKeith *et al.*, 2017). In the USA, only two of the three recommended biomarkers, dopamine transporter single positron emission tomography (DaTscan) or polysomnography to document presence of rapid eye movement sleep behaviour disorder are available to support a DLB diagnosis (in combination with one core clinical feature). ^{123}I-MIBG (^{123}I-metaiodobenzylguanidine) scanning has been approved by the United States Food and Drug Administration for the evaluation of pheochromocytoma and some forms of heart failure and has been recently incorporated as a supportive biomarker for clinical DLB diagnoses in the most recent revised DLB Consortium consensus criteria (McKeith *et al.*, 2017; Uyama *et al.*, 2017; Goldstein and Cheshire, 2018). Such a noradrenergic radioligand would be worthy of study to validate its use for diagnosing DLB, particularly in demented patients who do not have either cognitive fluctuations or visual hallucinations, and also lack parkinsonism or dream enactment behaviour.

Multiple studies have shown sympathetic cardiac denervation in subjects with Parkinson's disease, and similar trends in DLB, by the use of MIBG analysis or post-mortem cardiac analysis (Yoshita *et al.*, 1997; Yoshita, 1998; Goldstein, 2001; Orimo *et al.*, 2002, 2007; Fujishiro *et al.*, 2008; Orimo *et al.*, 2008). However, studies to date in DLB cases either lacked pathological confirmation or used limited numbers of post-mortem samples with no statistical analysis (Yoshita *et al.*, 2001, 2015; Orimo *et al.*, 2005; Takahashi *et al.*, 2015; Manabe *et al.*, 2017). To our knowledge, this is the first report with a substantial number of autopsied cases, and nerve bundles analysed, showing a statistically significant separation of AD/DLB cases from CN and Alzheimer's disease cases based on cardiac TH- and NF-immunoreactive nerve fibre density. Our results provide the physiological basis to justify further research on validation of cardiac nuclear imaging ligands for diagnosing DLB but it would not be likely to clinically separate ADLB from Alzheimer's disease subjects without a-syn. This is probably because, as for ILBD subjects, the peripheral spread and severity of a-syn pathology in these individuals is not yet as burdensome as it is in Parkinson's disease and DLB (Beach *et al.*, 2010). We also showed a significant negative correlation of TH fibre densities with a-syn densities in both

brain and heart. This supports previous observations and provides further evidence for a disease process wherein spread of a-syn pathology directly causes depletion of sympathetic nerve fibres from the myocardium (Yoshita *et al.*, 2001, 2015; Orimo *et al.*, 2002, 2008; Fujishiro *et al.*, 2008; Takahashi *et al.*, 2015; Manabe *et al.*, 2017). Importantly, our study provides autopsy evidence for sympathetic denervation of the heart in individuals with AD/DLB who were not formally diagnosed during life. Since Alzheimer's disease pathology in these subjects may lead to masking of core DLB features, and previous work using ^{123}I-MIBG has shown sympathetic denervation in clinically diagnosed DLB subjects, our data suggest that sympathetic nuclear imaging ligands are worthy of further study to better identify these mixed AD/DLB cases during life.

Supplementary material

Supplementary material is available at *Brain Communications* online.

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Competing interest

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