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Caudate nucleus volumes in stroke and vascular dementia

Jeffrey Chee Leong Looi [a,*], Vanessa Tatham [a], Rajeev Kumar [a], Jerome J. Maller [b,f], Ellen Millard [a], Wei Wen [c,d], Xiaohua Chen [c,d], Henry Brodaty [c,e], Perminder Sachdev [c,d]

[a] Research Centre for the Neurosciences of Ageing, Academic Unit of Psychological Medicine, Australian National University Medical School, Building 4, Level 2, The Canberra Hospital, P.O. Box 11, Woden Australian Capital Territory 2605, Australia
[b] Alfred Psychiatry Research Centre, Monash University, Melbourne, Victoria, Australia
[c] School of Psychiatry, Faculty of Medicine, University of New South Wales, Prince of Wales Hospital, Sydney, Australia
[d] Neuropsychiatric Institute, Prince of Wales Hospital, Sydney, Australia
[e] Primary Dementia Collaborative Research Centre, University of New South Wales, Sydney, Australia
[f] Centre for Mental Health Research, Australian National University, Canberrra, Australia

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ABSTRACT

We aimed to assess the volume of the nucleus caudatus as a neuroanatomical substrate of fronto-subcortical circuits, in stroke patients with/without dementia, and the relationship to potential determinants of neural circuit integrity such as white matter hyperintensities (WMH) and stroke volume. Stroke only (Stroke) ($n=19$) and stroke with Vascular Dementia (VaD) ($n=16$) and healthy control ($n=20$) subjects, matched on demographic variables, underwent extensive neuropsychiatric assessments and manual MRI-based volumetric measurements for intracranial area (ICA), stroke volume, and bilateral caudate volume. WMH on MRI were quantified using an automated algorithm. Multivariate analysis of covariance (controlling for age and ICA), revealed that across the three groups, caudate volumes were significantly different. There was a significant difference in bilateral caudate nucleus volume between subjects by diagnosis (Stroke, VaD, control). The control group was largest in overall mean volume of the diagnostic groups, followed by the Stroke group (86% of controls), and finally, the VaD group (72%). There was a partial correlation between total caudate volume and the total volume of deep WMH including periventricular regions and brainstem, controlling for ICA; and for total stroke volume. Stroke patients with VaD have smaller caudate nuclei compared to those without dementia and healthy controls, with the stroke-only patients being intermediate in their caudate volume status. There was preliminary evidence of negative correlation of caudate volume with volume of deep WMH and total stroke volume, suggesting cerebrovascular disease contributes to caudate atrophy, which, in turn may disrupt fronto-subcortical circuits.

1. Introduction

Vascular Dementia (VaD) is considered to be the second leading cause of dementia (Sachdev et al., 1999). Interest has focused on neuropathology that underpins the development of vascular dementia.

The caudate nucleus, in the basal ganglia, is a candidate region which is potentially vulnerable to ischemia and disconnection via damage to white matter (WM) due to cerebrovascular disease. The basal ganglia are part of the extrapyramidal motor pathways (Allen and Tsukahara, 1974). Functional magnetic resonance imaging (fMRI) confirms the roles that the caudate plays in cognition (Middleton and Strick, 1994; Seger and Cincotta, 2005), as have lesion studies of neuropsychiatric manifestations of basal ganglia disorders (Bhatia and Marsden, 1994; Ring and Serra-Mestres, 2002; Nishio et al., 2003). For example, subacute strokes in the caudate nucleus have been associated with perseveration independent of hemi-neglect (Nys et al., 2006).

The caudate nucleus has relevance as a neuroanatomical substrate of dysfunction in relation to frontal-subcortical circuits in stroke and vascular dementia. We previously suggested frontal-subcortical circuit dysfunction as the substrate of executive dysfunction in stroke, vascular cognitive impairment and post-stroke apathy (Looi and Sachdev, 2000; Brodaty et al., 2005). The caudate plays a crucial role in relaying inputs from the prefrontal cortex in animals and thus may be involved in processing higher executive cognitive functions associated with these regions (Alexander et al., 1986; Sachdev et al., 2004; Hannestad et al., 2006). Anatomical studies have shown the existence of functionally segregated projections from prefrontal and parietal association cortices to, primarily, the caudate nucleus (Parent and Hazrati, 1995). The ventral striatum, especially the caudate, is implicated in cognition (Clark et al., 2005). The extensive interconnections of the human caudate nucleus with the prefrontal cortex, temporal gyri, frontal eye fields, cerebellum and thalami have been

* Corresponding author. Tel.: +61 2 6244-3500; fax: +61 2 6244 4964.
E-mail address: jeffrey.looi@anu.edu.au (J.C.L. Looi).

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demonstrated using diffusion tensor imaging (Lehericy et al., 2004; Leh et al., 2007). Damage to such circuits may potentially disconnect and degrade cognition subserved by such circuits (Looi and Sachdev, 2000). WM comprises a likely site in which such disconnection may occur. Damage to fibres in circuits connecting to the caudate, may, via denervation, cause atrophy (Hannestad et al., 2006). Similarly, caudate atrophy occurs post-cingulotomy (Rauch et al., 2000). Therefore, functionally salient WM ischemic lesions may be reflected in reduced caudate volumes in stroke, vascular cognitive impairment, and late life depression (Hannestad et al., 2006). Similarly, any compromise of blood supply to the caudate, including that from perinatal and developmental causes, may thus result in reduced caudate volume (Looi et al., 2009). There is evidence of the salience of the caudate in cognition and evidence of associated neuropathology which may have a role in etiopathogenesis of cognitive changes in stroke and VaD.

The cognitive manifestations of VaD may be partly due to reduced striatal activity, and because the caudate nucleus relays input from frontal regions attributed to cognition, it may be a key structure affected. The frontal executive features that have specifically been implicated in VaD include declines in working memory, abstraction, reasoning, mental flexibility and fluency (Looi and Sachdev, 1999). We hypothesized that if the caudate is involved in the pathological process of VaD, it could be demonstrated quantitatively by a reduction in caudate volumes in comparison to matched controls, and that the volumes of caudate nuclei in stroke subjects without VaD should then be intermediate between these groups. Hemispheric differences will be analyzed, based upon previous studies that had found lateralized effects for caudate volume (Looi et al., 2008b, 2009).

We also hypothesized that WM lesions in regions adjacent to, or potentially connected to, the caudate may cause disconnection of the caudate from afferent or efferent tracts. We hypothesized that the volume of WM lesions in such regions may have a negative correlation with caudate volume.

Strokes may also cause disconnection, via damage to cortical or subcortical structures, including WM. Thus, another measure of the severity of cerebrovascular disease is stroke volume. In those with cerebrovascular disease, we hypothesized that stroke volume would be negatively correlated with caudate nucleus volume.

2. Methods

2.1. Sample

Subjects were randomly selected from the Sydney Stroke study cohort based upon availability of MRI at baseline and image quality for tracing, excluding those with a stroke in the caudate (Sachdev et al., 2004).

Subjects were recruited between May 1997 and June 2000. Subjects were aged 58–85 years, did not have a diagnosis of dementia or other neurologic disorder prior to the stroke, did not have severe aphasia as a significant limiting factor for assessment (a score of <3 on the Aphasia Severity Rating Scale of the Boston Diagnostic Aphasia Examination) (Goodglass and Kaplan, 1983), and were well enough to consent to participate. Subjects had a decline of <5 points on the 16-item IQCODE (Jorm and Jacomb, 1989) over the 5 years preceding the stroke, as rated by an informant who had a minimum of once weekly contact with the subject in this period. Healthy control subjects were unpaid volunteers, recruited from the same neighborhood as the stroke subjects, matched for age, and who had no history of stroke, or other neurologic or psychiatric disorder. An attempt was made to match the subjects on sex and years of education.

Fifty-five participants (36 male and 19 female) were categorized into three groups. The first group ($n=16$) comprised patients who had suffered a stroke and were diagnosed with VaD (VaD); the second group ($n=19$) included individuals who had a stroke (Stroke) but were without cognitive impairment; and the third group ($n=20$) comprised healthy controls.

2.1.1. Assessment

Stroke subjects had a baseline assessment within 1 week of admission to hospital, which included a detailed medical history and examination, history of risk factors for cerebrovascular disease and dementia, a functional assessment, and the Mini-Mental State Examination (MMSE) (Folstein et al., 1975). Between 3 and 6 months after the index stroke, a detailed neuropsychological assessment and medical and psychiatric examination were performed, and subjects had a brain MRI scan. The control group had a similar assessment performed in one stage.

2.1.2. Neuropsychological assessment

The battery comprised the following tests pertaining to various cognitive domains: verbal memory (Logical Memory [LM] I and II subtests from Wechsler Memory Scale-Revised [WMS-R]) (Wechsler, 1987); visual memory (Visual Reproduction [VR] I & II from WMS-R) (Wechsler, 1987); working memory (Digit Span backwards, Arithmetic from Wechsler Adult Intelligence Scale Revised [WAIS-R]) (Wechsler, 1981); attention (Digit Span forwards [WAIS-R]) (Wechsler, 1981); mental control (WMS-R) (Wechsler, 1987); language (15-item Boston Naming Test) (Mack et al., 1992); information processing speed (Trail Making Test Part A, Reitan and Wolfson, 1985, Symbol Digit Modalities Test [SDMT], Smith, 1991); visuoconstruction (Block Design [WAIS-R], Wechsler, 1981 and copying simple figures); praxis-gnosis (Western Aphasia Battery ideomotor apraxia subtest items, Kertesz, 1983, finger gnosis and stereognosis, Benton et al., 1983; Strub and Black, 1985); abstract reasoning (Similarities, Picture Completion [WAIS-R]) (Wechsler, 1981); mental flexibility (Color Form Sorting Text, Weigl, 1941, Trail Making Test Part B, Reitan and Wolfson, 1985); verbal fluency (phonemic [FAS], Benton and Hamsher, 1978, and semantic [animals], Morris et al., 1989). Mental flexibility and verbal fluency were together characterized as executive function. Premorbid ability was estimated using the National Adult Reading Test-Revised (NART-R) (Nelson and Willison, 1982). Trained clinical psychologists performed assessments. Subjects were given breaks where appropriate to minimize the effects of fatigue on performance. Subjects judged to be clinically depressed were not tested until their depression had been satisfactorily treated as judged by a total score on the Global Depression Scale of 5, a reduction in self-reported symptoms of depression, informant report, or further psychiatric assessment (Sachdev et al., 2004).

2.1.3. Medical and psychiatric assessment

Medical and psychiatric assessment comprised the following: medical history; functional assessment (Social and Occupational Functioning Scale [SOFAS], American Psychiatric Association, 1994), Activities of Daily Living [ADL] (Katz et al., 1963), and Instrumental ADL [IADL]) (Lawton and Brody, 1969); a standard neurologic examination (European Stroke Scale) (Hanston et al., 1994); and detailed psychiatric assessment (past psychiatric history, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV (First et al., 1997), 28-item General Health Questionnaire (Goldberg and Hillier, 1979), 15-item Geriatric Depression Scale (Sheikh and Yesavage, 1986), Hamilton Depression Rating Scale (Hamilton, 1960), and Neuropsychiatric Inventory (Cummings et al., 1994).

2.1.4. Stroke subjects and dementia diagnosis

The stroke subjects were part of a group of 10–20% of consecutive patients admitted to two large teaching hospitals affiliated with the University of New South Wales who had recently had an ischemic stroke as diagnosed by two neurologists independently. Exclusions were for various reasons e.g. prior dementia, too sick, non-English speaking etc. and refusal (Sachdev et al., 2004). An ischemic stroke was defined as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 h or