Psychoneuroendocrinology 78 (2017) 151–158

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

Associations between hippocampal morphology, diffusion characteristics, and salivary cortisol in older men

Simon R. Cox[a,b,c,*,1], Maria del Carmen Valdés Hernández[a,c,d,*,1], Jaeil Kim[e], Natalie A. Royle[a,c,d], Sarah E. MacPherson[a,b], Karen J. Ferguson[a,c,f], Susana Muñoz Maniega[a,c,d], Devasuda Anblagan[a,c,d], Benjamin S. Aribisala[d,g], Mark E. Bastin[a,c,d], Jinah Park[e], John M. Starr[a], Ian J. Deary[a,b], Alasdair M.J. MacLullich[a,f], Joanna M. Wardlaw[a,c,d]

[a] Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, UK
[b] Department of Psychology, University of Edinburgh, UK
[c] Scottish Imaging Network, A Platform for Scientific Excellence (SINAPSE) Collaboration, Edinburgh, UK
[d] Department of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, UK
[e] School of Computing, Korea Advanced Institute of Science and Technology (KAIST), Daejeon, South Korea
[f] Edinburgh Delirium Research Group, Geriatric Medicine, University of Edinburgh, UK
[g] Department of Computer Science, Lagos State University, Lagos, Nigeria

ARTICLE INFO

Article history:
Received 23 September 2016
Received in revised form 24 January 2017
Accepted 24 January 2017

Keywords:
Cortisol
MRI
Brain
Hippocampus
3D shape analysis
Ageing

ABSTRACT

High, unabated glucocorticoid (GC) levels are thought to selectively damage certain tissue types. The hippocampus is thought to be particularly susceptible to such effects, and though findings from animal models and human patients provide some support for this hypothesis, evidence for associations between elevated GCs and lower hippocampal volumes in older age (when GC levels are at greater risk of dysregulation) is inconclusive. To address the possibility that the effects of GCs in non-pathological ageing may be too subtle for gross volumetry to reliably detect, we analyse associations between salivary cortisol (diurnal and reactive measures), hippocampal morphology and diffusion characteristics in 88 males, aged ~73 years. However, our results provide only weak support for this hypothesis. Though nominally significant peaks in morphology were found in both hippocampi across all salivary cortisol measures (standardised β magnitudes < 0.518, $p_{uncorrected} > 0.0000003$), associations were both positive and negative, and none survived false discovery rate correction. We found one single significant association (out of 12 comparisons) between a general measure of hippocampal diffusion and reactive cortisol slope ($\beta = 0.290$, $p = 0.008$) which appeared to be driven predominantly by mean diffusivity but did not survive correction for multiple testing. The current data therefore do not clearly support the hypothesis that elevated cortisol levels are associated with subtle variations in hippocampal shape or microstructure in non-pathological older age.

1. Introduction

Glucocorticoid (GC) production is regulated by the hypothalamic-pituitary-adrenal (HPA) axis, activation of which coincides with a period of need that is normally followed by a return to lower levels. It exhibits a diurnal rhythm (highest just after waking, reducing to a nadir overnight) and can also be increased through reaction to systemic or perceived stress (followed by a swift return to basal levels following resolution of the stressor; Herbert et al., 2006). In humans, older age is related to altered diurnal and reactive profiles (Otte et al., 2005; Heaney et al., 2010), as well as structural brain changes. It has been posited that dysregulation of the HPA axis in old age may lead to chronically elevated GCs (cortisol in humans), which may exert deleterious effects on specific brain structures such as the hippocampus (Sapolsky et al., 1986; Landfield et al., 2007), yet current evidence among older humans is inconclusive. In rodent

* Corresponding author at: Department of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, 49 Little France Crescent, Chancellor's Building, Edinburgh, EH16 4SB, UK.
E-mail address: M.Valdes_Hernan@ed.ac.uk (M.d.C. Valdés Hernández).
[1] These authors contributed equally to the work.

http://dx.doi.org/10.1016/j.psyneuen.2017.01.027

models, prolonged exposure to repeated instances of restraint stress or exogenous steroids results in reduced synaptic and dendritic complexity in the hippocampus (Cook and Wellman, 2004; McEwen and Gianaros, 2010), a reduction in hippocampal volume and hippocampal cell death (Landfield et al., 1978; Sapolsky et al., 1986, 1990). Human Cushing's patients (whose primary characteristic is a chronic excess of GCs; Patil et al., 2007) exhibit general cerebral atrophy and hippocampal volume reductions (Starkman et al., 2001; Michaud et al., 2009; Toffanin et al., 2011), though it remains unclear the extent to which hippocampal atrophy is distinct from generalised brain changes.

In non-pathological groups of ageing humans, however, the evidence for significant associations between cortisol levels and hippocampal volume measures is limited. Increasing 24 h cortisol levels over a 5 year period was associated with decreases in hippocampal volume (n = 11; Lupien et al., 1998), yet results from subsequent studies are agnostic. Several studies with larger samples have found no significant relationship between hippocampal volume and cortisol levels, variously measured (Coluccia et al., 2008; Cox et al., 2015b; Gold et al., 2005; Kremen et al., 2010; MacLullich et al., 2005, 2006, 2012). In contrast, others report either a negative association between hippocampal volume and reactive cortisol (Sindi et al., 2014; n = 32), or with waking cortisol, only when accounting for some, but not other types of interleukin (Sudheimer et al., 2014; n = 28). A larger study reported that evening (but not morning) cortisol levels were associated with smaller hippocampal volume, but that this was not significantly greater than general effects on gray matter (Geerlings et al., 2015; n = 4244). In the same sample as in the current study, we previously found no association between hippocampal volumes and either diurnal (morning or evening) or reactive (start and end of a cognitive stressor) salivary cortisol measures (Cox et al., 2015b). One possible factor underlying the null findings in many of the analyses above could be that effects of cortisol on hippocampal structure may be more subtle than gross hippocampal volumetry can detect, especially among groups of relatively healthy, non-pathological groups.

To investigate this possibility, we analysed two alternative classes of hippocampal measurement which might detect such effects. First, we examine differences in hippocampal morphology to identify any systematic shape differences in particular anatomical subregions subfields (boundaries illustrated in Moretti et al., 2012). The distribution of mineralocorticoid and glucocorticoid receptors (to which GCs bind) varies across hippocampal subfields in humans (e.g. Seckl et al., 1991; López et al., 1998; Medina et al., 2013; Wang et al., 2013) and some rodent studies have identified effects of GC exposure specifically in subregions Cornu Ammonis (CA1) and CA3 only (reviewed in McEwen, 2007); hence it is plausible that humans may also exhibit regional associations with cortisol levels. Among healthy children (n = 17, age range 7–12 years; Wiedenmayer et al., 2006), higher cortisol levels were not associated with hippocampal volume, but were associated with outward deformations in the subiculum on the dorsal surface at the head of the right hippocampus and at the dentate gyrus, and with inward deformations along the lateral aspects of the medial hippocampal segment, though data in older humans is lacking. Second, we provide an exploratory analysis of hippocampal microstructure using indices from diffusion tensor MRI (DT-MRI). This imaging modality exploits the Brownian diffusion of water molecules within the cerebral region of interest. Molecular water diffusion is constrained by microstructural features of brain tissue, such as macromolecules, fibres, and membranes (Jones et al., 2013). Extracted diffusion characteristics include the average magnitude of water diffusion (mean diffusivity; MD) and its directional coherence (fractional anisotropy; FA), and is thought to provide information about local microstructural tissue architecture (Alexander et al., 2007). We note that the hippocampal formation is a complex, heterogeneous structure, which makes direct relationships between diffusion data and specific qualities of hippocampal microstructure difficult to interpret. Nevertheless, grey matter water molecule diffusion may be pertinent to brain and cognitive ageing. Several lines of evidence indicate that hippocampal diffusion may provide a more sensitive biomarker for age-related neurodegenerative disease (reviewed in Weston et al., 2015). In the same overall sample that we examine here, these measures reportedly exhibit stronger cross-sectional associations with cognitive ability in older age than hippocampal volume (Aribisala et al., 2014), suggesting that individual differences in hippocampal microstructure may be an informative biomarker in brain ageing research. Hippocampal mean diffusivity has been identified as potentially sensitive to cortisol levels, though in a smaller group with a wider age range (n = 58, Madsen et al., 2012) in which older participants were not well represented (<10 participants aged over 60 years). In summary, we investigate whether innovative neuroimaging techniques may identify subtler regional associations between cortisol and the hippocampus in non-pathological older age than gross volumetry can detect.

2. Methods

2.1. Participants

The participants were the same as those described previously (Cox et al., 2015a,b). Briefly, they were drawn from the second wave of the Lothian Birth Cohort 1936 (LBC1936) – a longitudinal ageing study of older community-dwelling adults, all of whom were born in 1936. Initially recruited at age 70 (Wave 1, n = 1091; Deary et al., 2007), they underwent a brain MRI scan about three years later at Wave 2 (age ~73). From this second wave, male participants (to eliminate any potential confound of gender in this modest sample size; Eisenberger et al., 2007) were invited to participate in a cortisol sub-study based on the following criteria: score ≥24 on the MMSE (Folstein et al., 1975), a score <11 on the depression facet of the Hospital Anxiety and Depression Scale (Snaith, 2003), no diagnosis of neurodegenerative disorders, no history of serious neurological event (as ascertained from the MRI scans by a consultant neuroradiologist; JMW), a complete MRI scan, and not taking any GC, antidepressant or any other prescribed medication (ascertained during a detailed medical interview) that is known to impact HPA axis functioning or hippocampal structure. Forty-eight reported a diagnosis of hypertension, 12 diabetes without complications, 34 hypercholesterolaemia and 35 a history of cardiovascular disease (including angina or myocardial infarction). Of the 118 eligible participants who were invited, 90 (mean age 73.3 years, ranging from 72.4 to 74.3) agreed and gave informed consent.

2.2. Cortisol

Circulating levels of cortisol in blood and saliva are well-correlated (Vining et al., 1983; Perogamvros et al., 2010), indicating the utility of saliva samples are acceptable (and less invasive) means of indexing free cortisol levels. Salivary cortisol sampling protocol has previously been described elsewhere (Cox et al., 2015a,b). Briefly, samples were collected using Salivette devices (Sarstedt, Numbrecht, Germany) and stored at −80 °C following collection prior to being shipped to Dresden LabService GmbH, Germany, for assay using a commercial immunoassay kit with chemiluminescence detection (IBL-Hamburg, Hamburg, Germany). Intra-assay variation was 5.1%. Correlation coefficients for regression lines were >0.99, consistent with typical international standards. All measurements are reported in nmol/l. Saliva