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Advanced magnetic resonance imaging and neuropsychological assessment for detecting brain injury in a prospective cohort of university amateur boxers

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ABSTRACT

Background/aim: The safety of amateur and professional boxing is a contentious issue. We hypothesised that advanced magnetic resonance imaging and neuropsychological testing could provide evidence of acute and early brain injury in amateur boxers.

Methods: We recruited 30 participants from a university amateur boxing club in a prospective cohort study. Magnetic resonance imaging (MRI) and neuropsychological testing was performed at three time points: prior to starting training; within 48 h following a first major competition to detect acute brain injury; and one year follow-up. A single MRI acquisition was made from control participants. Imaging analysis included cortical thickness measurements with Advanced Normalization Tools (ANTS) and FreeSurfer, voxel based morphometry (VBM), and Tract Based Spatial Statistics (TBSS). A computerized battery of neuropsychological tests was performed assessing attention, learning, memory and impulsivity.

Results: During the study period, one boxer developed seizures controlled with medication while another developed a chronic subdural hematoma requiring neurosurgical drainage. A total of 10 boxers contributed data at to the longitudinal assessment protocol. Reasons for withdrawal were: logistics (10), stopping boxing (7), withdrawal of consent (2), and development of a chronic subdural hematoma (1). No significant changes were detected using VBM, TBSS, cortical thickness measured with FreeSurfer or ANTS, either cross-sectionally at baseline, or longitudinally. Neuropsychological assessment of boxers found attention/concentration improved over time while planning and problem solving ability latency decreased after a bout but recovered after one year.

Conclusion: While this neuroimaging and neuropsychological assessment protocol could not detect any evidence of brain injury, one boxer developed seizures and another developed a chronic sub-dural haematoma.

1. Introduction

The sport of boxing is an emotive and contentious subject. Many medical and charitable organisations have called for an outright ban on both amateur and professional boxing. Campaigners against boxing have attracted widespread media coverage with articles in both the written press and broadcasting arena (McCabe, 2009; British Broadcasting Corporation (BBC), 1998). Counter-arguments from pro-boxing organisations emphasise the intensive medical monitoring of participants (ABAE, 2006) and a reduction in exposure to cumulative head injury with modern regulations (Clausen et al., 2005). There are also potential benefits of boxing on physical fitness and in providing a positive, disciplined training environment, which can be particularly valuable in socially deprived communities.

Despite the high level of scrutiny that boxing attracts, the scientific evidence that underpins regulation is far from comprehensive (Loosemore et al., 2007). A spectrum of brain injury has been described in boxers, ranging from post-concussive syndrome to chronic traumatic

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encephalopathy (CTE) and rare instances of life-threatening haemorrhage (Hart et al., 2012). Despite these methodological shortcomings, evidence suggests the development of CTE (or dementia pugilistica) in retired ex-professional fighters from the historical era of regulations (Roberts, 1969). Questions remain regarding why some participants develop CTE while others do not, whether some participants are able to tolerate repeated head injury, and if ultimately boxing has been made safe enough through modern regulations to prevent brain injury.

Modern neuroimaging techniques are an attractive tool to help improve our understanding of the pathophysiology involved in boxing related brain injury. Initially MRI was only used in boxing with small case series and limited analysis methods, which led to rather non-specific findings (Levin et al., 1987; Jordan and Zimmerman, 1988; Jordan and Zimmerman, 1990a; Haglund and Bergstrand, 1990; Holzgraefe et al., 1992; Hähnel et al., 2008; Hasiloglu et al., 2011). Increasingly sophisticated analysis methods of structural imaging data have been developed enabling measurement of grey matter thickness and density, subcortical volume changes, and white matter microstructure at the voxel level for the whole brain. Recent studies that have applied these methods to participants with concussion from a variety of different sports (predominantly American Football, Football, Ice Hockey, and Mixed Martial Arts) have revealed convergent trends for concussion exposure to be related to reduced cortical thickness (Koerte et al., 2015; Albaugh et al., 2015; Tremblay et al., 2013), smaller subcortical structure volumes (Bernick et al., 2015a; Singh et al., 2014), and altered white matter diffusion metrics (Lancaster et al., 2016; Meier et al., 2015; Stamm et al., 2015; Wilde et al., 2015; Tremblay et al., 2014; Shin et al., 2014; Bazarian et al., 2014; Hart et al., 2013; Virji-Babul et al., 2013). Additionally, these findings have often corresponded to impaired neuropsychological function but appear to be more persistent, suggesting a biomarker of longer-term structural alteration. Limitations of these studies often include unmatched control groups, cross-sectional or retrospective designs, and a lack of statistical power. Nevertheless, modern neuroimaging techniques now have an established sensitivity to detecting structural morphology alterations related to sports concussion.

We set out to test whether signs of brain injury could be found to develop over the short term in otherwise young healthy individuals taking up amateur boxing for the first time. In order to test for brain injury, we used an advanced magnetic resonance imaging (MRI) protocol and extensive battery of computerized neuropsychological tests. We planned to recruit participants from a local university amateur boxing club and follow them with three assessments (baseline, post-bout and one year follow-up) over approximately 18 months.

2. Materials & methods

2.1. Participants

Boxers were recruited from Cambridge University Amateur Boxing Club (CUABC). Recruitment began at the start of the academic year prior to commencing boxing training. All participants were members of the Amateur Boxing association of England (ABAE) and had undergone a satisfactory medical examination. Exclusion criteria included: any prior participation in boxing; any participation in contact sports (particularly martial arts or rugby) since age 18; any previous history of neurological disease, neurosurgery or psychiatric disorder; any history of claustrophobia; and any metal implants within the head or neck. Demographic information collected included age, gender and intelligence quotient (IQ) as measured by the National Adult Reading Test (NART).

Contemporaneous MRI from control participants, who were not participating in boxing, were included in a cross-sectional analysis at baseline.

Ethical approval for the study was obtained from the Cambridge Local Research Ethics Committee (REC number: 06/Q0108/161). Control participants were recruited under ethical approvals from the West London and Gene Therapy Advisory Committee National Research Ethics Service committee (11/H0707/9), and the Cambridge Local Research Ethics Committee (06/Q0108/303).

2.2. Assessment protocol

Following informed consent, assessments of boxers were performed on three occasions. The first, baseline assessment was completed prior to commencing sparring or training. The second, post-bout assessment was within 48 h after the first competitive bout. The final, one-year follow-up assessment was at approximately one year after the post-bout assessment.

2.3. Imaging parameters

Imaging was performed a Siemens Tim Trio operating at 3T at the Wolfson Brain Imaging Centre, University of Cambridge, UK.

A T1-weighted image was acquired with the MPRAGE sequence, with parameters: acquisition matrix size 256 × 256; field of view 256 mm × 256 mm; 1 mm slice thickness; repetition time, TR = 2300 ms and; echo time, TE = 2.98 ms.

Images sensitive to water diffusion were acquired in 63 non-collinear directions with $b = 1000 s/mm^2$, and two images without diffusion weighting, $b = 0 s/mm^2$. Each image was acquired parallel to anterior-posterior (AC-PC) commissural line using an echo-planar imaging (EPI) sequence, with parameters: matrix size 96 × 96; field of view 192 mm × 192 mm; 63 axial slices; slice thickness = 2 mm; TR = 7800 ms, TE = 90 ms.

Prior to data analysis, MRI scans were viewed independently by two consultant neuroradiologists, one blinded to the timing of the scan (i.e. baseline, post-bout or one year follow-up), and the other aware of the scan timing. Additional sequences available for clinical assessment included gradient echo, FLAIR, and T2.

2.4. Neuroimaging analyses

Methods are described briefly below: full details are presented in the Supplemental information. Cortical thickness was estimated in two ways, with each method undertaking dissimilar approaches to image processing of T1-weighted MRI. Automated volume based cortical thickness estimation was performed with Advanced Normalisation Tools (ANTS, http://www.stnava.github.io) (Avants et al., 2009; Tustison et al., 2013; Das et al., 2009) while surface based estimation of cortical thickness estimation was performed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) (Reuter et al., 2010; Ségonne et al., 2004; Fischl et al., 2002; Fischl et al., 2004; Sled et al., 1998; Fischl et al., 2001; Ségonne et al., 2007; Dale et al., 1999; Fischl and Dale, 2000; Dale and Sereno, 1993).

Estimates of grey and white matter volumes at each intracerebral location were from T1-weighted MRI with FSL-VBM (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLVBM (Douaud et al., 2007)), an optimized VBM protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004; Andersson et al., 2008a).

Voxelwise statistical analysis of white matter DTI metrics, specifically FA and MD data, was carried out using Tract Based Spatial Statistics (TBSS) (Smith et al., 2006a), part of FSL (Smith et al., 2004; Smith et al., 2006b; Andersson et al., 2008b; Rueckert et al., 1999)

2.5. Neuropsychological assessment

Participants were asked to perform a series of neuropsychological tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB, Cambridge Cognition, Cambridge, United Kingdom; http://www.cambridgecognition.com). The tests were computerized and run on a Paceblade touch-screen computer with responses registered via