NeuroImage

www.elsevier.com/locate/ynimg
NeuroImage 25 (2005) 1175–1186

Voxel-based morphometry and stereology provide convergent evidence of the importance of medial prefrontal cortex for fluid intelligence in healthy adults

Qi-Yong Gong,[a,b,c,*] Vanessa Sluming,[a,b] Andrew Mayes,[d] Simon Keller,[a,b] Thomas Barrick,[a] Enis Cezayirli,[a] and Neil Roberts[a]

[a]Magnetic Resonance and Image Analysis Research Centre (MARIARC), University of Liverpool, UK
[b]Department of Medical Imaging, University of Liverpool, 2nd Floor, Johnston Building, P.O. Box 147, Liverpool L69 3BX, UK
[c]Clinical MR Research Centre (CMRRC), Department of Radiology, West China Hospital, Sichuan University, PR China
[d]School of Psychological Sciences, University of Manchester, UK

Received 23 August 2004; revised 20 November 2004; accepted 17 December 2004
Available online 25 February 2005

We investigated whether a relationship exists between frontal lobe volume and fluid intelligence as measured by both Cattell's Culture Fair test and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Performance scale, but not with crystallized intelligence as measured by the WAIS-R Verbal scale, in healthy adults, using two well-established image analysis techniques applied to high-resolution MR brain images. Firstly, using voxel-based morphometry (VBM), we investigated whether a significant relationship exists between gray matter concentration and fluid intelligence on a voxel-by-voxel basis. Secondly, we applied the Cavalieri method of modern design stereology in combination with point counting to investigate possible relationships between macroscopic volumes of relevant brain regions defined as dorsolateral, dorsomedial, orbitolateral, and orbitomedial prefrontal cortex on the basis of neuroanatomical landmarks, and fluid intelligence. We also examined the effect on these relationships of normalizing regional brain volumes to intracranial volume. VBM analysis revealed a positive correlation between gray matter concentration in the medial region of prefrontal cortex and Culture Fair scores (corrected for multiple comparisons), and also WAIS-R Performance Intelligence sum of scaled scores (SSS) (uncorrected for multiple comparisons before controlling for age, and this converges with the stereological finding of the positive correlation between volume of dorsomedial prefrontal cortex normalized to intracranial volume and Culture Fair scores after controlling for age. WAIS-R Verbal Intelligence SSS showed no correlations. We interpret our findings, from independent analyses of both VBM and stereology, as evidence of the importance of medial prefrontal cortex in supporting fluid intelligence.

Keywords: MRI; Voxel-based morphometry; Stereology; Intelligence; Brain volume

Introduction

How the brain supports intelligence can be explored by examining the effects on intelligence of focal brain lesions and by examining which brain regions activate when intelligence is exercised, but it can also be examined by determining whether variations in the volume of any brain region correlate with individual differences in intelligence in healthy individuals. Whereas functional neuroimaging does not establish the causal role of an activated region in intelligence, lesion evidence provides strong support for this claim, and the "neophrenological" approach does so as well, albeit more weakly and indirectly. It is assumed that MRI-derived measures of the volume of a particular brain structure in healthy brains are at least partially determined by the number and size (hence, the complexity of the synaptic connections) of the neurons that it contains so that greater volumes should mean that a structure works more efficiently (Andreasen et al., 1993; Bigler et al., 1995; Rushton and Ankney, 1995). Accordingly, it is plausible to hypothesize that, unless greater volume primarily reflects inadequate pruning of neurons in development (Howard et al., 2000) and other factors, such as the efficiency of neurotransmission, are fairly constant, individuals with larger brain regions should perform the functions mediated by those regions better.

Although most leaders in the field of intelligence have refused to give precise "meaning-style" definitions of the term (Deary,

* Corresponding author. Department of Medical Imaging, University of Liverpool, 2nd Floor, Johnston Building, P.O. Box 147, Liverpool L69 3BX, UK. Fax: +44 151 794 5766.
E-mail address: qiyong.gong@liverpool.ac.uk (Q.-Y. Gong).

1053-8119/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2004.12.044

2000), intelligence must depend on the cognitive abilities needed to solve a range of problems, such as defining words, ordering a related series of pictures, and indicating the odd one out among a set of words or pictures. The psychometric approach uses standardized tests to measure how well individuals solve problems like these. A century of research has shown that individuals' scores on different intelligence tests inter-correlate positively, and factor analysis has given rise to the notion that human intelligence is a multilevel hierarchy of abilities with a general factor or *g* at the top and more specific ability factors lower down the hierarchy (see Neisser et al., 1996 for a discussion). Identification of whether there are different, specific neural bases of the putative components of intelligence will help confirm or indicate the need for modifying the "unitary process" interpretation of these statistical conclusions.

Investigations of the neural bases of human intelligence have generally supported the view that greater brain size correlates positively with intelligence (Andreasen et al., 1993; Plomin and Kosslyn, 2001; Tisserand et al., 2001), although not all studies have provided positive results (Tramo et al., 1998). Even so, the earlier studies did not provide consistent evidence for the appealing notion that the volumes of *specific* brain regions correlate positively with intelligence or specific intelligence factors (Flashman et al., 1998; MacLullich et al., 2002). Recently, however, Thompson et al. (2001) identified a significant association between total gray matter volume of frontal cortex and a proxy measure of the general intelligence factor, *g*. This association is consistent with evidence that patients with large frontal lobe lesions showed marked impairments in those kinds of intelligence, sometimes referred to as fluid intelligence, that load highly on *g*, and relate to the ability to solve relatively novel problems which cannot be solved through the routine use of heavily overlearned cognitive routines (Duncan et al., 1995).

Fluid intelligence contrasts with crystallized intelligence or the ability to solve those more familiar kinds of problem that can be solved through the routine use of heavily overlearned cognitive routines. Crystallized intelligence typically loads more weakly on *g* (Gray and Thompson, 2004), and, unlike fluid intelligence, which tends to decline with age, it is relatively stable as age increases (Neisser et al., 1996). There is mixed evidence that fluid and crystallized intelligence are supported by partially distinct brain structures. Thus, although Duncan et al. (1995) found that frontal lesions probably do not disrupt crystallized intelligence whilst greatly disrupting fluid intelligence, the results of functional imaging are harder to interpret (see Gray and Thompson, 2004 for a discussion). As both kinds of intelligence load on *g*, they may well depend on one or more common processes that involve working memory and/or attentional control, although fluid intelligence should rely on these processes more. However, fluid intelligence may also depend on processes not needed for crystallized intelligence. Thus, some frontal cortex regions may be selectively critical for identifying what kind of more familiar problem a novel problem resembles and others may be key for monitoring the effectiveness of the routines consequently applied so as to be prepared, if necessary, to adopt a more appropriate analogy and its corresponding routines.

Given its large volume, which constitutes a substantial part of the whole neocortex, it would not be surprising if different parts of the frontal neocortex each supported distinct cognitive functions relevant to novel problem solving. Efforts are therefore being made to further localize a possible focus for fluid intelligence within this large volume of prefrontal lobe. It has been shown that greater volume in a region of medial prefrontal cortex was associated with increased IQ in a healthy pediatric population (Wilke et al., 2003). This is partially consistent with the results of three PET imaging studies that found a significant role for prefrontal cortex in performing tasks which depend strongly on fluid intelligence (Duncan et al., 2000). Although, relative to more routine tasks using matching materials, the three different kinds of novel problem solving (loading highly on *g*) only showed overlapping activations in the lateral frontal cortex, solving novel visuospatial problems also activated medial prefrontal cortex. More recently, Gray et al. (2003) showed, in an event-related functional magnetic resonance imaging (fMRI) study of 48 subjects, that the positive relationship between fluid intelligence and performance on high versus low interference lure trials of a three-back working memory task was mediated by the greater neural activity in the lateral frontal cortex and parietal cortex bilaterally produced by successful performance on the high interference lure trials. As high interference trials demand high levels of attentional control, a plausible explanation of the results is that the use of fluid intelligence critically involves certain kinds of attentional control, and that more efficient use of this control, which leads to higher fluid intelligence, depends on greater activation in key structures including the lateral frontal cortex.

Gray and Thompson (2004) discuss some possible reasons why Gray et al. (2003) and Duncan et al. (2000) partially conflict. One reason is that functional imaging studies cannot directly establish that activity in a brain region is causally critical for a cognitive process. It is therefore of interest to investigate whether in healthy adults individual differences in the size of lateral and/or medial frontal regions as well as the parietal sites also identified by Gray and his colleagues correlate with differences in fluid and crystallized intelligence, or only with differences in fluid intelligence. Finding frontal correlations only with fluid intelligence would provide support for the view that activity in one or more of these regions fairly selectively supports fluid intelligence as a function of increasing size.

In the present study, we have applied two well-established brain image analysis techniques to test the structural relationship between gray matter in prefrontal cortex and performance on Cattell's Culture Fair test and the Wechsler Adult Intelligence Scale-Revised (WAIS-R) measures of Performance and Verbal intelligence. Cattell's test is the best measure of fluid intelligence, the WAIS-R Performance tests probably depend on both fluid and crystallized intelligence, but the WAIS-R Verbal tests probably depend most on crystallized intelligence (Duncan et al., 1995; Woodcock, 1990). The Cattell and WAIS-R Performance tests directly tap the ability to solve different kinds of visuospatial problems, but it is probable that all three kinds of test tap verbal abilities to some extent because these abilities are used to solve visuospatial as well as verbal problems. Our primary aim was to determine whether fluid and crystallized intelligence correlated differently with the size of brain regions (particularly in the frontal lobes) after correcting for age-related changes. To achieve this primary goal, we also had the subsidiary aims of identifying: (i) the relationship between age and fluid and crystallized intelligence; (ii) age-related changes in the size of brain regions, particularly those in the frontal lobes; and (iii) whether (voxel-based morphometry) VBM-based frontal gray matter density correlations corresponded to stereology-based prefrontal subfield volume correlations.