OPINION

The structural basis of inter-individual differences in human behaviour and cognition

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Abstract | Inter-individual variability in perception, thought and action is frequently treated as a source of 'noise' in scientific investigations of the neural mechanisms that underlie these processes, and discarded by averaging data from a group of participants. However, recent MRI studies in the human brain show that inter-individual variability in a wide range of basic and higher cognitive functions — including perception, motor control, memory, aspects of consciousness and the ability to introspect — can be predicted from the local structure of grey and white matter as assessed by voxel-based morphometry or diffusion tensor imaging. We propose that inter-individual differences can be used as a source of information to link human behaviour and cognition to brain anatomy.

We all appreciate the substantial differences among our friends and colleagues in their ability to see, think and act, and such variability introduces a rich diversity of culture and lifestyle into our society. In the neuroscience of human behaviour and cognition, inter-individual differences are often treated as a source of 'noise' and therefore discarded through averaging data from a group of participants. Moreover, university students of industrialized Western countries are typically the participants in many psychology and neuroscience studies[1]. Despite the narrow selection of human diversity in such experiments, it is widely assumed that the conclusions drawn from a small sample generalize to the entire population. However, inter-individual differences can be exploited to understand the cognitive processes underlying such behaviours[2].

FIGURE 1 illustrates the sort of dataset that is typically used in behavioural experiments, in which responses — such as reaction times, perceptual thresholds or blood oxygenation level-dependent (BOLD) signals — show differences between two experimental conditions. Researchers typically focus on the change in the mean response associated with

an experimental manipulation or behaviour (FIG. 1a). Such averaging of data across participants is performed to reveal underlying effects despite the presence of measurement

noise. However, this averaging ignores a large variation in individual responses (FIG. 1a, right panel). In this example, two participants (pink lines) show an opposite trend from that of the other participants and two participants (green lines) show much larger responses than other participants. These differences are typically viewed as measurement errors or as uninteresting peculiarities of individuals, and are therefore discarded. However, if they are highly consistent across different tests, then they are characteristics of the individuals and may ultimately reflect differences in their brain function. Moreover, as FIG. 1b makes clear, systematic patterns of inter-individual differences (in this case, half the sample showing an opposite response to that of the other half) can be dissociated from differences in mean activity (which are absent in this example).

In some areas of psychology, such as personality and intelligence research, the main focus has been on inter-individual differences. However, this potentially powerful approach has been almost completely neglected for many years in studies of the neural basis of more basic cognitive functions, such as perception and motor
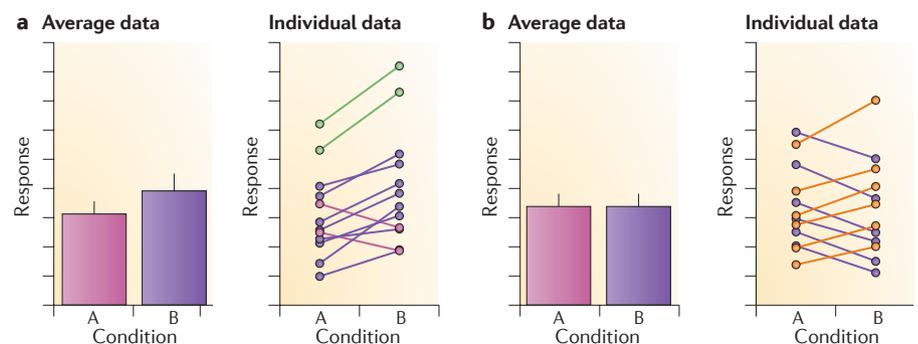
Figure 1 | **Examples of typical average and individual responses across two conditions. a** | The mean responses for two conditions are illustrated in the left panel. In this example, the response in condition B is significantly larger than in condition A ($P < 0.01$). Error bars indicate one standard error of the mean ($n = 12$). Individual data comprising the mean responses are shown by lines in the right panel. Although the overall trend is consistent with the mean values (purple lines), some participants showed opposite trends (pink lines) and others showed much higher responses (green lines). Such inter-individual differences are masked by averaging but could be attributable to variability of brain function. **b** | The mean responses between conditions A and B do not show a difference. However, the underlying individual data could be divided into two groups of participants showing opposite trends (orange and purple lines). In such cases, the mean results would be uninformative, but specifically studying the cause of the opposite trends between the two groups could reveal relevant brain structures.

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control. These studies have mostly focused on commonalities across individuals and thus often neglect inter-individual differences. This may reflect the fact that, in everyday life, inter-individual differences in basic functions such as vision and action are less noticeable (unless there is a clear pathological deficit) than differences in personality traits or intelligence, and this has lead to an assumption that the neural bases of such basic functions are less variable across individuals.

In this Perspective, we argue that a large amount of phenotypic information about the neural basis of human behaviour and cognition can be obtained by specifically studying inter-individual variability. As visual and motor cortices are arguably the most well-characterized regions in neuroscience, studying the neural basis of inter-individual differences in perception and motor behaviour could be a fruitful approach to understanding how structural differences affect the capacity of the brain regions involved.

Methods that provide measures of neural activity (such as functional MRI (fMRI)[3–12], electroencephalography (EEG)[13–19], positron emission tomography[20–23] and magnetic resonance spectroscopy[24–26]) have been used to study the neural bases of individual differences in cognition. However, here we focus on the recently growing body of evidence that inter-individual variability in a wide range of human behaviours can be predicted from the structure of grey matter and white matter tracts of the human brain measured with MRI (BOX 1).

Most anatomical MRI studies have focused on differences in brain structure between groups of experts in a particular domain and groups of non-experts. People with specialized skills such as musicians[27,28], London taxi drivers[29], or Italian bilinguals[30] have markedly developed brain structures in specific brain regions associated with their expertise. But experts are by definition extremes in the general population, and there is increasing evidence that anatomical MRI can detect more subtle inter-individual differences even within groups of non-experts. We therefore review studies that specifically examine inter-individual differences within a population of healthy adults, rather than the extensive literature comparing neuroanatomical differences between particular groups (for example, those with neurological and psychiatric diseases) and healthy volunteers.

Motor behaviour and decision making

Perhaps the simplest action that can be taken in response to a visual stimulus is to press a button. Reaction times vary according to whether the responding hand is contralateral or ipsilateral to the stimulated visual field, which has been attributed to timing delays associated with the need for inter-hemispheric neural signalling when the responding hand is contralateral to the stimulated visual field. Inter-individual differences in this interhemispheric transmission time are reflected in the microstructural integrity of the corpus callosum, assessed by diffusion tensor imaging (DTI), in healthy volunteers[31] and individuals with schizophrenia[32].

Other simple motor paradigms also show inter-individual variability associated with differences in brain structure. For example, variability in choice reaction time (that is, the time taken to indicate a choice, usually by pressing a button) across individuals correlates with fractional anisotropy of the optic radiation[33] (FIG. 2a) as measured by DTI (BOX 1). With regard to more complex motor coordination, inter-individual differences in the skill of a bimanual coordination task are reflected in the differences in the integrity of the part of the corpus callosum that links supplementary motor areas[34]. Moreover, inter-individual variability in the ability to select the correct response in the presence of response conflict correlates with the grey matter density of the pre-supplementary motor area (pre-SMA)[35] (FIG. 2b). Thus, it seems that inter-individual variation in both the initiation and the cognitive control of simple and complex motor tasks is reflected in the structural anatomy of the brain.

In decision making, fast decisions often come at the cost of reduced accuracy[36,37]. This phenomenon is termed the speed–accuracy trade-off and has been observed in many decision-making tasks[38–41]. Thus, when faster responses are required, one needs to flexibly adjust the decision criterion. There are considerable inter-individual differences in the ability to flexibly adjust the speed–accuracy trade-off, and this variability correlates with connection strengths between the pre-SMA and striatum, as measured using DTI[42] (FIG. 2c). This finding is compatible with earlier functional MRI studies showing, first, that the areas connected by this pathway are activated by cues that indicate

higher demands for response speed; and second, that activation in these areas correlates with the ability to switch between cautious and risky behaviours[43]. These studies of inter-individual differences also suggest that the cortico–basal ganglia circuitry regulates the speed–accuracy trade-off.

As these examples illustrate, studies of inter-individual differences are not limited to explaining the neural basis of performance differences between individual participants, but can be exploited to reveal the circuitry associated with a particular cognitive function.

Perception

The existence of inter-individual variability in psychophysical thresholds for sensory discrimination has been known for many years, as has that of inter-individual variability in the size of components of early sensory processing pathways, such as the lateral geniculate nucleus and primary visual cortex in the visual pathway[44,45]. The size of the surface area of the primary visual cortex that is devoted to processing visual signals from a particular part of the visual field varies as a function of eccentricity from fixation, and this relationship can be characterized by the cortical magnification factor[46]. In humans, inter-individual variability in the visual acuity threshold correlates with this cortical magnification factor, establishing a link between variability in perception and brain structure[47]. However, such a relationship was established in studies in which both perception and physical stimulation varied at the same time. More recent work has sought to dissociate perception and physical stimulation, establishing a link between sensory awareness and brain structure, as discussed below.

Perceptual rivalry. When visual input has conflicting interpretations (for example, the Necker cube), conscious perception can alternate spontaneously between the competing interpretations. Such spontaneous fluctuations of conscious perception can be used to delineate the neural basis of conscious perception[48], because the subjective perception fluctuates while the physical stimulation is constant. Surprisingly, there is great inter-individual variability in the rate at which these spontaneous alternations occur[49,50]. A recent study tested whether an individual's 'perceptual switch rate' was reflected in their cortical thickness, local grey matter volume and/or white matter integrity. All of these measures of brain structure converged to show that the structure of
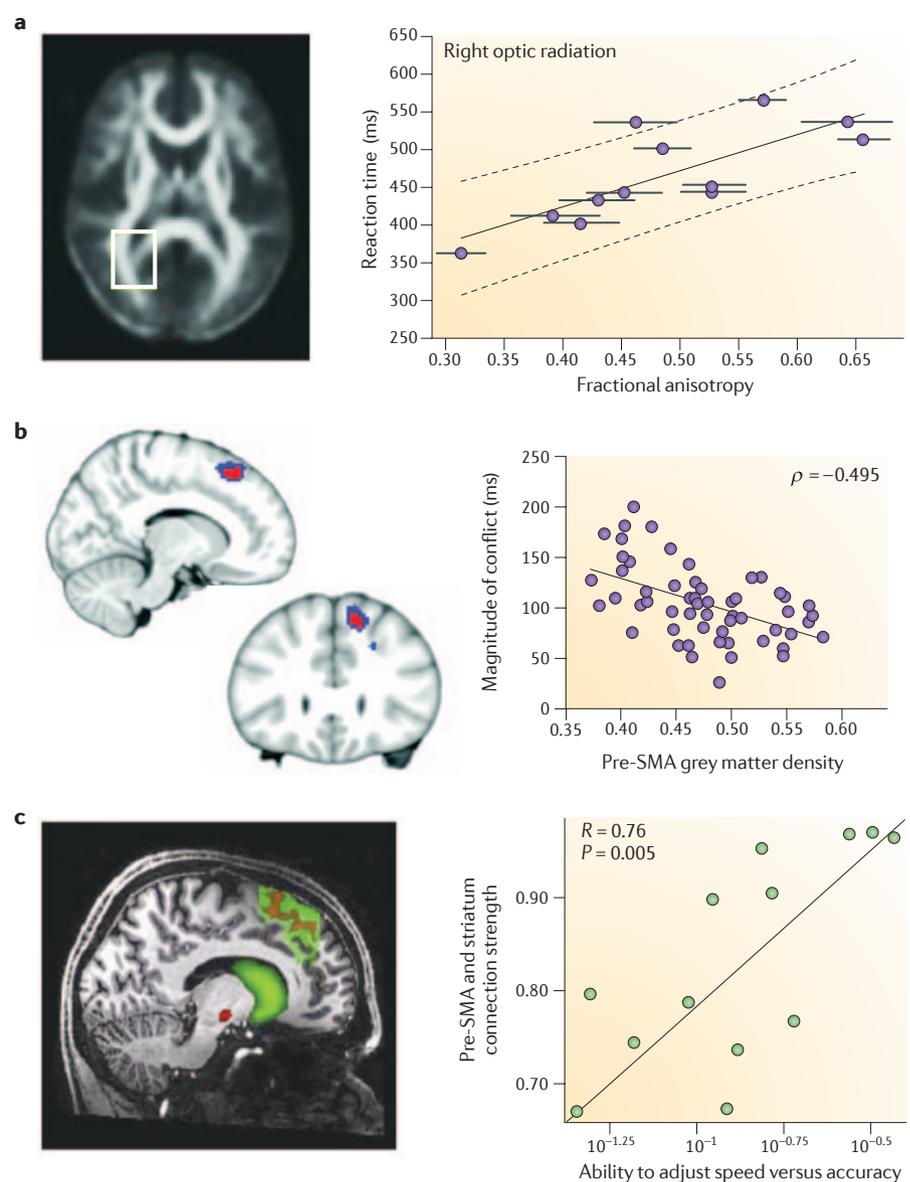
Figure 2 | Structural bases of inter-individual differences in action and decision making. a | The speed of reaction time in making a visual choice correlates with the fractional anisotropy (a measure of white matter integrity) of the right optic radiation (indicated by the white box). **b |** Grey matter density of the pre-supplementary motor area (pre-SMA) correlates with the degree of the response conflict effect. The scatter plot shows the correlation in the condition in which conflicting response tendencies were elicited consciously (because the conflicting stimuli were only weakly masked). **c |** Connection strength between the pre-SMA (upper green area in the left panel) and striatum (lower green area in the left panel) correlates with individuals' ability to adjust the speed–accuracy trade-off. Part **a** is modified, with permission, from REF. 33 © 2005 National Academy of Sciences. Part **b** is modified, with permission, from REF. 35 © 2011 MIT Press. Part **c** is modified, with permission, from REF. 42 © 2010 National Academy of Sciences.

the bilateral superior parietal lobes (SPLs) can account for inter-individual variability in perceptual switch rate. Specifically, individuals with a fast switch rate have thicker and larger volume SPLs than individuals with a slow switch rate, and the white matter underlying the SPLs has a higher integrity. This correlation of SPL structure with individuals' switch rates suggests that

these bilateral regions are involved in triggering spontaneous perceptual switches[51]. Furthermore, the anterior part of the right intraparietal sulcus (IPS) shows an opposite correlation — that is, the larger the grey matter volume of this area, the slower the switch rate (FIG. 3a). The opposing influences of the SPLs and the anterior IPS suggest that these areas might have complementary roles, with
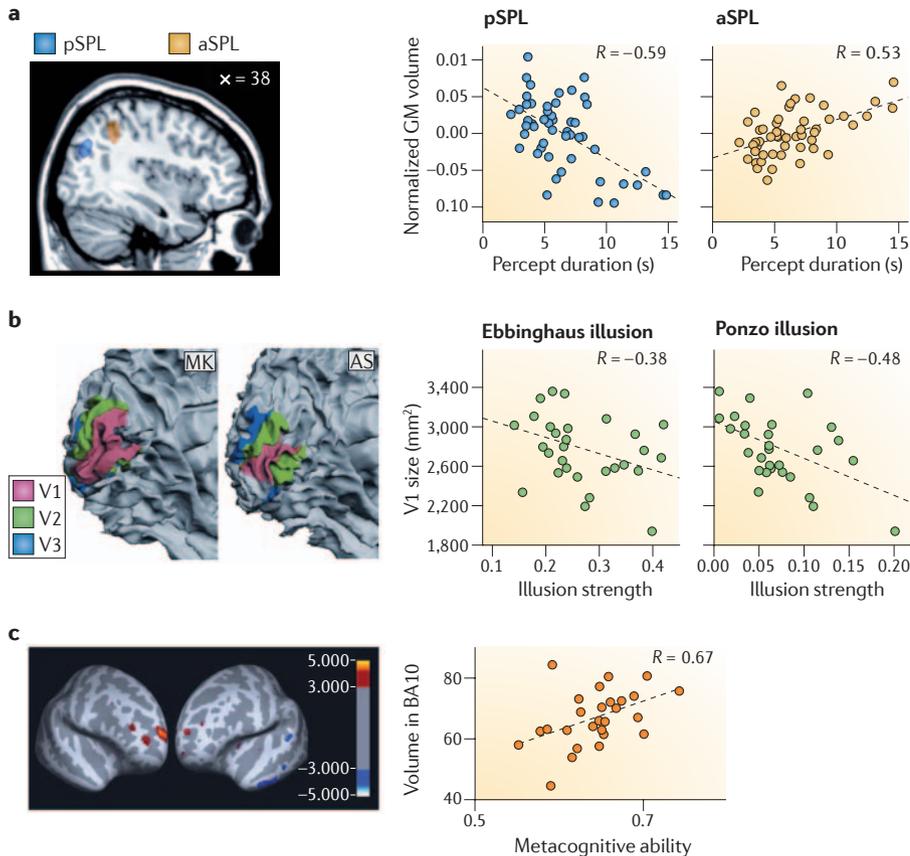
Figure 3 | Structural bases of inter-individual differences in conscious perception. a | Structural correlates of inter-individual differences in the duration of one percept in a perceptual rivalry task (in which a single visual input can have conflicting interpretations) (left panel). A larger posterior superior parietal lobe (pSPL) was associated with a slower rate of switching between competing interpretations of a visual input, whereas a larger anterior superior parietal lobe (aSPL) was associated with a faster switch rate. Data in the middle and right panels are from REF. 51 and REF. 52, respectively. **b |** The surface areas of visual cortical areas V1, V2 and V3 from two example participants (left panels). A larger V1 was associated with weaker Ebbinghaus and Ponzo illusions (right panels). **c |** A structural correlate of metacognitive ability (left panel). Statistical T-maps for positive ('hot' colour map: red, orange and yellow) correlations and negative ('cool' colour map: blue) correlations between grey matter volume and metacognitive ability are projected onto an inflated cortical surface. Better metacognitive abilities were associated with a larger Brodmann area 10 (BA10), an area in the rostral prefrontal cortex (right panel). The left panel of part **a** is reproduced, with permission, from REF. 52 © 2011 Cell Press. Part **b** is reproduced, with permission, from REF. 60 © 2011 Macmillan Publishers Ltd. All rights reserved. Part **c** is modified, with permission, from REF. 80 © 2010 American Association for the Advancement of Science.

the SPLs detecting possible alternative perceptual interpretations, and the anterior IPS sustaining the current percept[52].

The parietal cortex areas in which structural variation is associated with perceptual switch rate are similar to the regions that are activated when perceptual switches occur[53–56]. Previously, it was unclear whether the functional role of these parietal structures was related to the active triggering of perceptual switches[53,57] or instead to sustaining the current percept[58,59]. The anatomical studies described above, corroborated by complementary transcranial magnetic stimulation (TMS) experiments[51,52], suggest that the parietal cortex contains different subregions associated with both proposed functions.

Despite earlier findings[53–56] that prefrontal cortical regions are also activated during perceptual switches, anatomical studies[51,52] have not found a neural correlate of perceptual switch rate in prefrontal regions. Whether this dissociation indicates that inter-individual differences in switch rate are attributed only to the parietal, but not to the frontal, cortex remains to be determined, as the inability to identify structural correlates in the prefrontal cortex could simply be a matter of statistical power.

Sensory awareness. Subjective awareness of physically identical visual stimuli can also vary across different individuals. For example, individuals with colour blindness perceive colours differently to those with normal vision. This raises the possibility that even individuals with normal vision may show variability in how they perceive the world. Although it is difficult to directly compare the subjective experiences of different people, inter-individual differences in the perceived strength of a perceptual illusion — whereby physically identical stimuli produce perceptually different appearances depending on their local context — can be quantitatively compared. In a study that compared individuals' susceptibility to geometrical visual illusions (the Ponzo and Ebbinghaus illusions), just such variability in illusion strength was found[60]. Moreover, the strength of the illusion correlated negatively with the size of early retinotopic visual area V1, but not visual area V2 and visual area V3 (REF. 60) (FIG. 3b; see BOX 2 for possible mechanisms mediating such correlation).

Retinotopic mapping techniques using fMRI allow delineation of borders between early visual areas, and close relationships between anatomical folding patterns and retinotopic representations of early visual areas have been reported[61]. By contrast, a purely anatomical measure of the surface area of the peri-calcarine cortex (where V1 is located) does not correlate with the illusion strengths[60]. This suggests that the size of the surface areas of visual regions (as determined by fMRI[62]) reflect an individual's visual experience much more sensitively than crude gyral and sulcal anatomy alone. In non-visual cortical regions, it is generally difficult to estimate the size of the surface areas of functionally segregated areas because it is difficult to unambiguously delineate the borders between them. For subcortical regions, however, the size can be unambiguously estimated on the basis of structural MRI measurements (for example, the size of the amygdala or hippocampus[63–65]). It is thus possible to establish the relationship between the size of such regions and inter-individual variability in cognition and behaviour. For example, the size of the amygdala correlates with inter-individual differences in memory[66], social phobia[67] and social network size[68].

The grey matter density in the calcarine sulcus (plus the auditory cortex) is also associated with inter-individual differences in synaesthetic experiences, in which a particular stimulus evokes a sensory experience in addition to the modality-typical sensory experience[69]. Grapheme–colour synaesthesia

— in which letters and numbers are associated with certain colours — is one of the most common types of synaesthesia. There are two types of grapheme–colour synaesthetes: 'projectors' see the associated colour in the external world, whereas 'associators' experience the colours in their mind. Projectors have more grey matter in the calcarine sulcus and the prefrontal cortex than associators, and associators have more grey matter in the hippocampus and angular gyrus than projectors. These findings suggest that the experiences of associated colours in the external world in projector synaesthetes may be mediated by the primary sensory cortex.

Metacognition. Metacognition, or 'cognition about cognition', refers to the ability to comment or report on one's own mental state[70] and is often considered the touchstone of the presence of consciousness in humans[71–74] and animals[75,76]. In the context of sensory processing, we can be correct or incorrect in our perceptual judgments, but we can also provide a metacognitive estimate of our confidence each time we make such a judgment. The ability of different individuals to accurately link confidence and performance — that is, their metacognitive ability — can be formulated and quantified using the so-called type 2 performance in signal detection theory[77,78].

Substantial inter-individual differences exist in metacognitive ability[79]. A recent voxel-based morphometry (VBM) study revealed that metacognitive ability — defined operationally as the ability to appropriately link insight (confidence) to objective performance in a perceptual decision-making task — is reflected in the grey matter volume of the rostral prefrontal cortex and precuneus[80] (FIG. 3c). Fractional anisotropy in the genu of the corpus callosum also correlates with metacognitive ability, suggesting the importance of white matter connections linking the rostral prefrontal cortex to other cortical regions[80].

These three studies of inter-individual differences in visual awareness suggest that, although the architecture of the basic visual pathways must be similar among healthy individuals, differences in their subjective experiences can be attributed to regionally specific morphological differences in the brain.

Attention. The ability to control attention to relevant tasks varies considerably across individuals. The attention network test (ANT) is widely used to assess three dissociable aspects of attention: executive control, orienting and alerting[81,82].

Box 2 | What mechanisms might link the size of the sensory cortex with awareness?

In the Ebbinghaus illusion (see the figure, part **a**), the two orange disks are exactly the same size, but the left disk is perceived to be smaller than the right disk because of the surrounding 'inducers'. The magnitude of this illusion can be quantified by measuring how much the sizes of the disks need to be physically changed for the two disks to appear to be the same size. The magnitude of this size illusion varies considerably across individuals and such variability correlates with the size of the functionally defined surface area of the primary visual cortex (V1). What might be the mechanism that links the size of V1 to illusion strength?

This relationship may be understood in terms of scaling principles of overall brain size[178]. As a neocortical area such as V1 becomes larger, the spatial extent of neurons needs to become larger to maintain the same extent of visual field coverage (from the red neuron in the small V1 to the blue neuron in the large V1 in part **b** of the figure). However, increases in the size of neurons negatively affect the electrical conduction properties of the dendrites and axons, because the electrical signal in the dendrite attenuates as a function of distance. To maintain the same signal conductivity in larger neurons, the diameter needs to be disproportionally thicker with increases in length: if dendrites are twice as long in a large neuron, then the dendrites need to be four times as thick as the original neuron to maintain the same conductivity properties. However, the cost of compensation by increasing dendrite thickness is high and the increase in the size of neurons is therefore biophysically limited. This scaling principle suggests that the size of neurons is not proportionally scaled to the size of brain areas. Thus, the increase in the extent of dendrite arborization is comparatively smaller as brain size increases[178]. This implies that, in a larger V1, the lateral spread of dendrites covers a proportionally smaller area in retinotopic space than in a smaller V1 (the red neurons in part **b** of the figure), and the spatial extent of lateral interaction becomes weaker (see the corresponding shrinkage of visual field coverage by the neuron of the same size (right panel). Thus, the scaling principle could explain the weaker illusion strength in individuals with a large V1 as it implies that lateral interactions would be weaker in a larger V1. Although this hypothesis can offer a possible explanation for the observed size–percept relationship, the idea presented here remains speculative. Thus, further investigations in animal models and using post-mortem histology are needed to understand how differences in macroscopic brain structure, such as grey matter volume or cortical surface area, might be translated into differences in microstructure, such as the size of neurons or the degree of myelination (see the subsection 'Microstructural basis of MRI'). Figure is modified, with permission, from REF. 178 © 2000 Springer.

a Ebbinghaus illusion

b Cortical surface area   Visual field

Large V1

Small V1
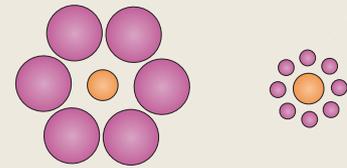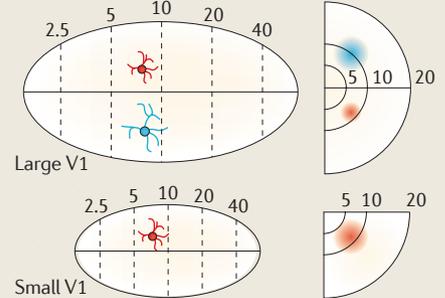
Cortical thickness in several brain regions is positively correlated with the executive control and alerting (but not the orienting) components of attention[83]. Specifically, the executive control component of attention is reflected in the thickness of the anterior cingulate cortex, the right inferior frontal gyrus and left medial frontal areas extending to the frontal pole and dorsolateral prefrontal cortex. By contrast, the alerting component of attention is negatively correlated with the thickness of the left superior parietal lobe extending to the precuneus. These findings of structure–cognition relationships illustrate that individual differences in attentional networks can be mapped onto differences in grey matter brain structure.

Functional neuroimaging studies have implicated areas in attentional control that are broadly similar to those that show inter-individual variability in structure. For example, the anterior cingulate cortex and the right inferior frontal gyrus are activated during the ANT[84] and in tasks that involve conflict monitoring and response inhibition (types of executive control)[85,86], and the alerting component of the ANT is associated with activation of the left superior parietal cortex. However, dissociations between structural and functional findings are also observed. For example, the alerting component of the ANT induced stronger activation in brain regions the thickness of which does not correlate with attentional performance,

such as the right superior temporal gyrus[84]. Such differences may arise because the structural MRI analyses reviewed here focus on the variability that gives rise to inter-individual differences in behaviour, whereas fMRI studies typically reveal the most consistent activation of brain regions across individuals. A direct comparison of inter-individual differences in fMRI signals with VBM within the same participants will be important for understanding the relationship between functional and structural MRI results[87–90].

Intelligence and personality

Economic motivation and decision making. In addition to simple decision-making behaviour (discussed above), more complex motivation and decision-making processes show correlations with brain structure. For example, inter-individual differences in delay-discounting behaviour (the tendency to prefer receiving small, immediate rewards over large, delayed rewards) are correlated with white matter integrity in frontal and temporal lobe white matter tracts in 9–23-year-olds[91].

The idea that delay-discounting behaviour in children is reflected in the development of connections within the prefrontal cortex[91] is consistent with the involvement of the prefrontal cortex in this type of behaviour. For example, higher BOLD responses are observed in the prefrontal cortex when adult participants choose a delayed rather than an immediate reward[92]. Similarly, the association of the integrity of white matter tracts in the temporal lobe with delay-discounting behaviour[91] is consistent with studies showing that rats with hippocampal damage choose immediate rewards in delay-discounting tasks[93].

Intelligence and information processing speed. In contrast to the study of motor behaviour or visual perception, the psychology of human intelligence has a long tradition of specifically investigating individual differences in humans, and there is a rich literature on this topic. The cognitive neuroscience of intelligence is beyond the scope of this Perspective and has been reviewed elsewhere[94].

Some examples of the correlation of brain structure with measures of intelligence include structural MRI studies that show that inter-individual variability in intelligence correlates with cortical thickness[95–98] and white matter integrity, as assessed with DTI[99–102]. Moreover, a global network parameter that is derived from

white matter tractography and reflects network efficiency is correlated with intelligence[103], suggesting that the degree to which white matter connectivity can support efficient information processing may be important for intelligence. Information processing speed, assessed by simple reaction tasks, is associated with intelligence[104,105]. In healthy older people, a general factor associated with white matter integrity (across eight major white matter tracts quantified using probabilistic tractography techniques) predicts information processing speed[106].

Personality. In psychology, many questionnaires have been devised to measure personality traits. Personality psychologists often use a model called the 'Big Five'[107] to describe the fundamental dimensions of personality traits; these comprise neuroticism, extraversion, openness, agreeableness and conscientiousness. Differences in these broad factors and their narrower facets across individuals have consequences on everyday behaviour[108] and in cognitive tasks[109–111]. Moreover, up to half of the variability in these five personality traits is heritable[112,113], suggesting that inter-individual differences in these traits have biological bases in the brain[114]. In addition, the high degree of heritability in such psychological constructs indicates the biological relevance and validity of psychometrics, and thus motivates further investigation of their relationship to the brain.

As with research on intelligence, personality psychology has a long tradition of studying inter-individual differences. However, investigations into the structural bases of the Big Five personality traits have started only recently (FIG. 4). One study found that anatomical variability in specific brain regions predicts inter-individual differences in personality traits[115]. Specifically, extraversion correlates positively with grey matter volume in the medial orbitofrontal cortex. By contrast, neuroticism correlates negatively with grey matter volume in the right dorsomedial prefrontal cortex and left medial temporal lobe, and correlates positively with grey matter volume in the mid cingulate cortex. Agreeableness correlates positively with grey matter volume in the posterior cingulate cortex and correlates negatively with that in the superior temporal sulcus and fusiform gyrus. Conscientiousness correlates positively with grey matter volume in the lateral prefrontal cortex. However,

openness does not show statistically significant correlations with grey matter volume in any given region. Similarly, brain structure correlates of more specific traits such as impulsivity (as measured by the Barret Impulsivity Scale) have been found in the orbitofrontal cortex[116]. Variation in the volume of the orbitofrontal cortex is also related to variability in emotion regulation and affect[117].

Neuroanatomical investigations into the biological basis of personality traits measured by self-report questionnaires may in the future provide a solid ground for traditional personality psychology, which currently relies heavily on semantic description and the participants' ability to estimate their own personality (that is, metacognition). Furthermore, questionnaire-based approaches to probing brain structure may allow a set of questions to be devised the answers to which predict the size of brain structures of interest. For example, it is possible that an individual's answer to the question "Are you scared of snakes?" may predict the size of the amygdala — a key region for processing fear memories — of that individual. Such approaches may reveal links between a brain region and its function in everyday life. A crucial challenge for brain structure analyses will be the ability to predict an individual's ability or personality better than self-report questionnaires. Self reports reflect a range of cognitive biases (such as overestimation known as the Kruger-Dunning effect[118]), and structural MRI data could potentially offer less biased information about an individual's personality trait. At present, no direct comparison between a questionnaire and brain structure measurements has been reported. However, such comparisons will be crucial to test brain-based descriptions of personality traits in future.

Social cognition. Humans are social animals, but they show variability in the degree to which they engage in social activity. The volume of the amygdala correlates with the size and complexity of social networks in adult humans[68], and there are relationships — albeit weaker — between variables reflecting the structure of an individual's social network and cortical thickness in three cortical areas connected with the amygdala[68]. Thus, even complex psychological concepts such as the construction and maintenance of social networks have a correlate in brain structure.
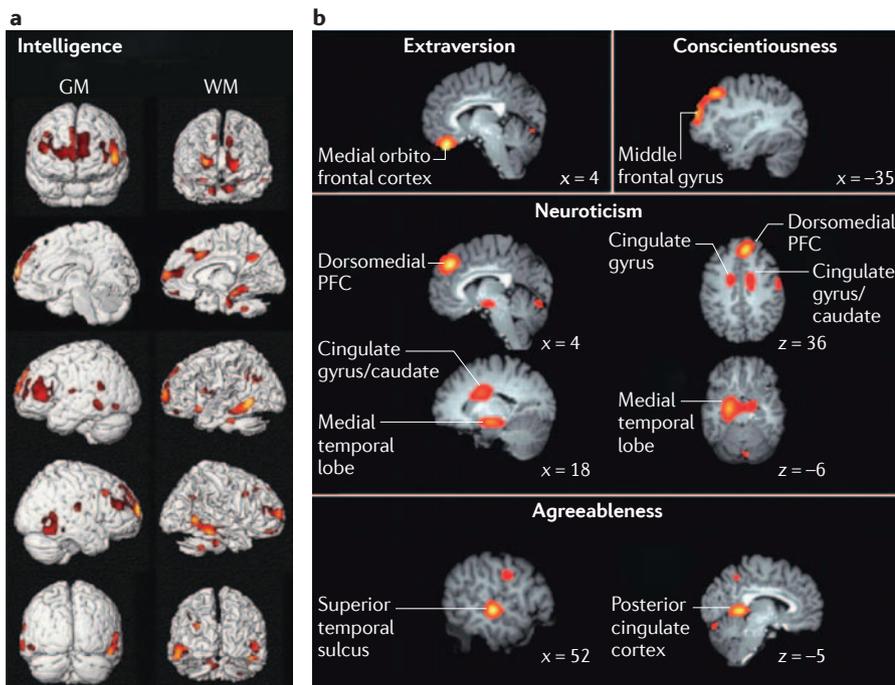
Figure 4 | **Brain structure correlates of higher cognitive functions. a** | Grey matter (GM; left panel) and white matter (WM; right panel) correlates of general intelligence. Greater grey matter and white matter volumes in specific brain areas are associated with higher intelligence. **b** | Grey matter correlates of the Big Five traits. Grey matter volume in specific cortical areas correlates with scores on a specific trait. PFC, prefrontal cortex. Part **a** is reproduced, with permission, from REF. 125 © 2004 Elsevier. Part **b** is modified, with permission, from REF. 115 © 2010 Sage Publications.

Genetic and plasticity effects on anatomy

Studies in monozygotic and dizygotic twins have shown that grey matter volumes of the prefrontal and temporal cortex are strongly influenced by genetic factors[119], whereas other areas are less strongly affected. This suggests that the heritability of a particular cognitive function depends on the extent to which the relevant cortical regions are influenced by genetic factors[120–122]. Genetic factors contribute to cortical thickness and surface area size independently[123]. Such genetic contributions to variations in brain structure may underlie heritability of cognitive abilities such as the intelligence quotient (IQ)[97,124–128].

Although early stages of brain development are mediated by genetic programmes[129,130], later stages of development, as well as brain organization and brain maturation, result from interactions between genetic and environmental factors[131,132]. Indeed, recent VBM findings indicate that brain structure is not determined solely by genetic factors but is extensively modulated by experiences such as prolonged training[133–138]. For example, training on a visual motor coordination task, such as learning to juggle, has a measurable effect on grey matter volume of visual motion processing area V5 and the posterior parietal cortex[133,135] as

well as white matter integrity of neighbouring fibres that presumably mediate visuospatial transformation[138]. Moreover, such structural plasticity can be demonstrated in the adult brain across training periods as short as 90 minutes over 2 weeks[139].

Moreover, compared with carefully matched, illiterate controls, individuals who have learned to read for the first time as adults have greater grey matter volume in the bilateral angular, dorsal occipital, middle temporal, left supramarginal and superior temporal gyri[140] (see also REF. 141). These areas are associated with crucial functions for literacy such as semantic, phonological and high-level visual processing[142,143] and highlight the possibility that plastic structural changes in the adult human brain are associated with training.

Correlations in performance across tasks

In structural MRI studies, such as those discussed above, measurements of brain structure can be performed separately from measurements of behavioural performance, which can occur outside the MRI scanner using conventional behavioural or psychological tasks. This separation offers the opportunity to study the relationship between brain regions and relatively static

properties of an individual's characteristics, such as personality traits. By contrast, functional neuroimaging studies using fMRI and EEG require task designs that evoke activation in the brain in a manner that is relevant to the trait of interest (for example, REFS 4,10), which can be difficult. Thus, an important advantage of neuroanatomical studies of inter-individual differences (over studies using fMRI or EEG) is that they allow one to link an individual's performance or trait as measured in an ecologically valid environment (that is, outside an MRI scanner) to brain structure measurements obtained in an MRI scanner.

It is conceivable that inter-individual differences in performance on a single task can be mapped onto the structure of a single brain region, but such a simplistic notion of a one-to-one mapping between a cognitive function and the structure of a brain region needs to be examined carefully. As has been shown in many functional neuroimaging studies, a single region can be involved in a broad range of tasks. Thus, it is unlikely that there is always one core region that is crucial for a particular cognitive function. Instead, a region with a structure that correlates with a behavioural measure needs to be interpreted in the context of the known functions of the region and its role in other, related behavioural tasks.

The separation of behavioural measurements from structural measurements of brain anatomy also permits multiple tasks to be administered to the same set of participants. One successful approach to analysing the correlations between related cognitive tasks uses principal component analysis or factor analysis. For example, research into the principal factors in working memory and attentional tasks has characterized how different aspects of working memory and attention correlate with each other[144]. Moreover, the components derived from such an analysis can subsequently be used to determine whether the structure of particular brain areas is associated with each component in a VBM analysis. Such a combined approach of factor analysis and VBM has been successfully applied to face perception in individuals with developmental prosopagnosia[145]. This multivariate approach to analysing behavioural data is a promising way to address correlations between different tasks, as it can potentially reveal common underlying components and any neural substrates. Such an approach may provide new insights into how different cognitive functions are related to each other and which regions underlie those functions.

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Glossary

Corpus callosum
A white matter structure that connects the left and right cerebral hemispheres.

Cortical magnification factor
The size of the surface area of the visual cortex relative to the size of the visual field it represents. It is generally larger for the central part of the visual field near the fovea and smaller for higher eccentricity.

Decision criterion
An evaluative criterion used for selecting one option from several possible actions or percepts.

Developmental prosopagnosia
A congenital impairment in the ability to recognize faces without any deficit in recognizing other categories of objects.

Eccentricity from fixation
The distance of a given position in the visual field from the point of fixation (that is, the centre of the visual field). Eccentricity is usually measured in degrees of visual angle.

Fractional anisotropy
A scalar measure of directionality of diffusion of water molecules derived from a collection of diffusion-weighted images. It is thought to reflect regional white matter features such as axon calibre, fibre density and myelination that are associated with white matter integrity.

Multiple-comparison problem
The high probability of obtaining a false-positive result when multiple inferential statistical tests are conducted in parallel (for example, across many voxels). Statistical methods to address this problem require a strong level of evidence to detect genuine relationships.

Optic radiation
A bundle of white matter fibres that relays visual information from the lateral geniculate nucleus to the visual cortex.

Response conflict
A situation in which an automated response competes with a voluntary choice of task-relevant action.

Signal detection theory
A theoretical framework to compute the ability to discriminate a signal from noise.

Type 2 performance
A measure of the ability to discriminate correct responses from incorrect responses using introspection or subjective confidence.

A disadvantage of studies that relate brain structure to behaviour is that the data are temporally unchanging, except when specifically studied through characterization of anatomical changes associated with learning or development. This contrasts with the temporally dynamic nature of functional neuroimaging data, which allows researchers to investigate how activation patterns change over time across the brain and to characterize functional interactions between distant brain regions. However, there have been attempts to reveal network structures in the brain by examining the structural covariation of brain regions[146–148]. Such analyses of structural covariance across the brain may offer the possibility of characterizing individuals in terms of network strengths instead of voxel-based local volumes.

Limitations of current research
Microstructural basis of MRI. Understanding the cellular basis of local changes in grey matter volume is necessary for a better interpretation of VBM studies. However, the microstructure and cellular events that give rise to a global quantity that can be measured by structural MRI remain poorly understood. One possibility is that differences in grey matter volume reflect underlying synaptogenesis and dendritic arborization, which in rats are known to vary markedly between animals reared in environments of different levels of complexity[149,150]. Such experience-dependent formation and elimination of synapses continues into adulthood in rodents[151].

The radial unit hypothesis put forward by Rakic suggests that neurons within the same cortical column have a common developmental origin and migrate along the same pathway from the ventricular zone[131,152,153]. Before migration starts, progenitor cells undergo symmetrical cell division and increase the number of the radial columns in the ventricular zone. This process has consequences for the allocation of cortical columns and regional surface areas in the mature cortex. By contrast, the thickness of the cortex is determined by the number of cells produced by asymmetrical cell divisions within the ontogenic columns[152,153]. These two stages of cellular events (that is, symmetrical and asymmetrical cell divisions) are likely to be controlled by different sets of genes. Consistent with this model, cortical thickness and surface area size are independently heritable in humans[123]. The radial unit hypothesis provides an important framework for understanding how individual differences in cortical thickness and surface area may be determined by genetic and developmental processes.

However, a direct link between microstructures and macrostructures has not been established in the human brain. A histological study directly compared whether histopathological measurements of resected temporal lobe tissue correlated with grey matter density as used in typical VBM studies[154]. However, none of the histological measures — including neuronal density — showed a clear relationship with the grey matter volume[154]. We suggest that determining the microscopic neuronal structures that give rise to macroscopic structural differences will be an important step towards understanding how volumetric measures of the brain structure translate into differences in computational capacity. However, different populations should be compared with caution, as the microstructural events that correlate with a cognitive function may differ between, for example, healthy and diseased or young and old individuals. Some VBM studies show a negative correlation between grey matter volume and cognitive performance (BOX 3). To interpret such seemingly paradoxical results, it will be important to investigate how macroscopic volumetric measures are reflected in microstructures at the cellular level.

From correlation to causation. In general, when we try to relate inter-individual differences to brain structure using VBM, we face a massive multiple-comparison problem. This requires both a large sample of participants (typically tens to hundreds of participants) and fairly high correlations between brain structure and behavioural data to achieve conventional levels of statistical significance with appropriate correction for multiple comparisons. The upper limit of any correlation is constrained by the reliability of both behavioural and MRI measurements, and this reliability can be assessed by test–retest consistency in the same participants. Thus, improving the behavioural measurements could improve the sensitivity of VBM analysis.

As with studies investigating brain activation using fMRI, VBM studies of brain anatomy are intrinsically correlational. They can only show an association between the structure of a particular brain region and some behavioural performance. Such correlational associations do not necessarily imply causal relationships, and there are also chances of false discoveries due to the highly multidimensional nature of such correlational analyses.

To complement such correlational analyses, we suggest that intervention studies using brain stimulation techniques such as TMS and transcranial direct current stimulation (tDCS) can provide independent support for a causal link between structure and function. For example, in the VBM studies
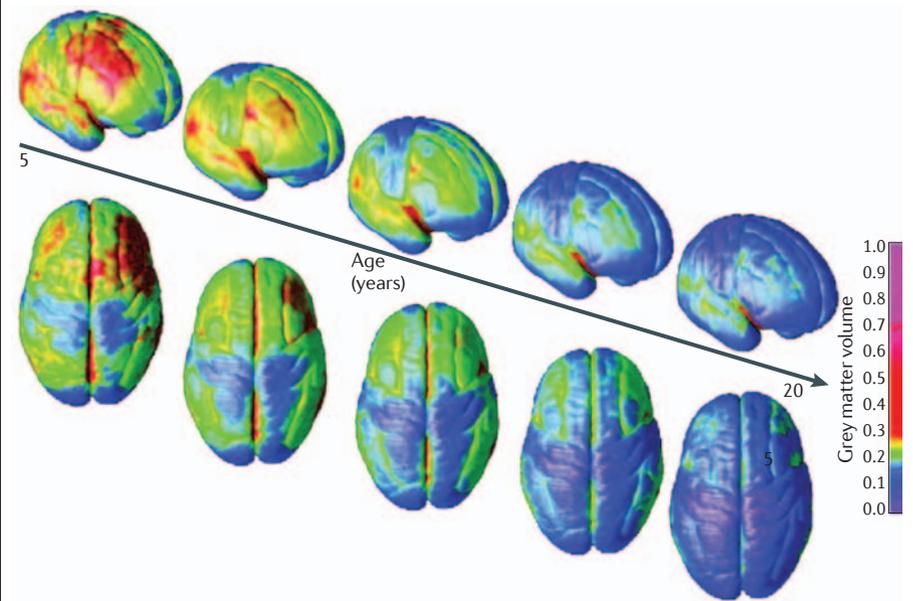
of perceptual rivalry described above[51,52] (FIG. 3a), we first identified cortical regions the structure (that is, cortical thickness) of which correlated with individuals' switch rates between competing perceptions, and then used TMS to confirm that those regions have a causal role in generating switches. Correlations between the thickness or size of a brain structure and performance on a task of interest can be used to generate new hypotheses as to which brain areas might be crucial for the performance of the task. The functional involvement of those areas in the task can subsequently be confirmed (or disproved) by disrupting the function of those regions with intervention methods such as TMS and tDCS.

It is often assumed that there is a close relationship between changes in brain structure measured using structural MRI, and changes in brain activity measured using fMRI. However, such a close relationship remains to be demonstrated. The cellular basis of the changes underlying VBM findings associated with structural MRI is uncertain, and BOLD fMRI signals can in certain circumstances be dissociated from patterns of neuronal spiking[155–159]. It is thus conceivable that individual differences in anatomical structure and BOLD activity may be dissociated for components of brain networks associated with certain behaviours. We suggest that understanding the relationship between inter-individual differences in brain structure and brain function may be a rich area for future research.

Conclusions and future directions

Investigations of inter-individual differences in human behaviour show that surprisingly rich information about individuals is encoded in their brain anatomy and can be measured using non-invasive structural MRI. There has been a rapid growth in the number of studies examining inter-individual differences in human behaviour and its association with structural features of the brain. Associations between white and grey matter anatomy and behaviour are not confined to motor behaviour and motor learning, but extend into domains of sensory perception and many areas of higher-order cognition. This has identified a number of crucial issues for future work to address: first, cross-sectional studies do not distinguish between the possibilities that brain structure varies in response to behavioural variability or vice versa. Longitudinal or interventional studies are required to help parse causality between brain structure and behaviour. Second, the time course of structural plasticity needs to

be addressed. In the motor domain, a surprising amount of short-term plasticity (over a few weeks) in brain structure is apparent. The degree to which other aspects of inter-individual variability in perception or higher cognitive processes are susceptible to similar plasticity is an intriguing topic for future development. Third, the predictive power of

brain anatomy for evaluating brain structural correlates of individual differences needs to be established more fully. Recent efforts to predict clinical phenotype from brain anatomy in autism spectrum disorders[160] and Alzheimer's disease[161] highlight the potential for using brain anatomy as an aid to clinical diagnosis. This raises the question of how

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Box 3 | **Is more grey matter always associated with better performance?**

It is often assumed that a larger cortical volume or greater grey matter density is associated with better computational efficacy of that region. Many examples discussed in this Perspective are consistent with this view. However, there are cases in which lower cortical volume is associated with better task performance. For example, in individuals afflicted with congenital amusia — a difficulty in detecting pitch change in melody — the cortex is larger and thicker in the right inferior frontal gyrus and in the secondary auditory cortex[179,180]. Similarly, the ability to manipulate self-generated thoughts improves during adolescence, and this is associated with a decrease in grey matter volume of the rostrolateral prefrontal cortex[181]. Moreover, people who are easily distracted in everyday life have a larger left superior parietal lobe than those who are not easily distracted[182].

This inverse relationship between structure and performance might be explained from a developmental perspective. During adolescence, the synapses in the cortex undergo pruning[183], and the computational efficacy of cortical regions is thought to improve after the pruning process by removing weak synapses[184]. Also, the number of neurons decreases with maturation of the brain[185]. Macroscopic reduction in grey matter density can be observed non-invasively in the human brain[186–191]. Loss of grey matter volume initially begins in primary sensory and motor areas in early childhood and then spreads to the frontal and parietal cortex (see the figure, which shows a reduction of grey matter volume in the age range of 5–21 years old). The reduction in grey matter volume is thought to reflect synaptic and/or neuronal pruning processes and to underlie maturation of the cortex. Considering cortical pruning as a process of removing inefficient synapses and neurons, it is conceivable that a smaller volume (or lower grey matter density) as a consequence of the synaptic pruning leads to more efficient processing.

However, this is only one aspect of the capacity–volume relationship. Macroscopic grey matter volume measured by MRI consists of various substructures, such as neuronal cell bodies, dendrites, axon terminals and glial cells. How the amount and balance of these microstructures translates into the computational capacity of the cortex is unclear. For example, it is possible that grey matter with more neurons and grey matter with fewer synapses could both lead to a good performance. In such a situation, the balance between different constituents of grey matter would be as important as volume. Future research will need to address the relationships between microstructures and the computational capacity of the cortex. Figure is reproduced, with permission, from REF. 185 © 2004 National Academy of Sciences.

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much behavioural variability in healthy humans can be predicted on an individual (or group) basis from brain anatomy; and whether such variability can (or should) have an application. Fourth, the microstructural basis of MRI structural differences needs to be determined. The relatively poor understanding of the structural basis underlying differences detected by VBM and other MRI-based techniques will remain a limitation until its cellular basis is better characterized. The lack of inter-individual variability in animal models may present a difficulty in addressing this question.

In this Perspective, we have argued that inter-individual differences in behaviour, often discarded by averaging data across participants, can be a rich and important source of information and can be exploited to reveal the neural basis of human cognition and behaviour in general. We suggest that the future directions outlined above will be important areas of research to build the foundations of this emerging area of research.

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