

Mapping Brain Development and Aggression

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ABSTRACT

Introduction: This article provides an overview of the basic principles guiding research on brain-behaviour relationships in general, and as applied to studies of aggression during human development in particular. **Method:** Key literature on magnetic resonance imaging of the structure and function of a developing brain was reviewed. **Results:** The article begins with a brief introduction to the methodology of techniques used to map the developing brain, with a special emphasis on magnetic resonance imaging (MRI). It then reviews briefly the current knowledge of structural maturation, assessed by MRI, of the human brain during childhood and adolescence. The last part describes some of the results of neuroimaging studies aimed at identifying neural circuits involved in various aspects of aggression and social cognition. **Conclusion:** The article concludes by discussing the potential and limitations of the neuroimaging approach in this field.

Key Words: children, adolescents, magnetic resonance imaging, frontal cortex, social cognition.

RÉSUMÉ

Introduction: Cet article se veut un survol des principes fondamentaux utilisés dans l'étude des relations entre système nerveux central et comportements, et plus spécifiquement dans l'application de ces études aux comportements d'agression durant les diverses phases du développement du cerveau. **Méthodologie:** Nous avons passé en revue les principaux articles de la littérature sur l'imagerie cérébrale traitant des structures et des fonctions du cerveau au fur et à mesure de sa maturation. **Résultats:** Nous nous pencherons d'abord sur les techniques utilisées pour identifier les aires cérébrales. Nous étudierons en second lieu les connaissances actuelles sur la maturation des structures telle qu'observée par imagerie cérébrale chez l'homme durant l'enfance et l'adolescence. Nous terminerons par les résultats d'études dont le but était d'identifier les circuits neuronaux sous-jacents à des comportements d'agression et à la cognition sociale. **Conclusion:** Nous discuterons du potentiel et des limites de l'imagerie cérébrale dans l'étude de l'agression et de l'identification des aires cérébrales au fur et à mesure de la maturation du système nerveux central.

Mots-clés: L'enfants, adolescentes, l'imagerie cérébrale traitant, cognition sociale.

BRAIN-BEHAVIOUR RELATIONSHIPS

The chief motivation for brain mapping studies is identification – in time and space - of neural circuits associated with particular sensory, motor and cognitive functions. Although the initial research has been focused on the healthy brain of an adult individual, neuroimaging is also beginning to make inroads into the research of normal and abnormal brain development: unravelling the details of structural and functional maturation of various neural systems represents a first step towards the understanding of the biological underpinnings of cognitive development in health and disease. A wide range of brain-mapping techniques is available today, including positron emission tomography (PET), functional magnetic-resonance imaging (fMRI), electroencephalography (EEG), magnetoencephalography (MEG), and transcranial magnetic stimulation (TMS). These methods allow the researcher to measure (PET, fMRI, EEG, MEG) and to manipulate (TMS) neural activity in the human brain; they differ in spatial and temporal

resolution, nature of the measured signal, as well as in the extent of brain coverage. Given its non-invasive nature, MRI represents the most common techniques employed for developmental studies of brain structure and function, and will be considered in this review. The reader interested in the other techniques is referred to other publications (e.g. Paus 2003, Walsh and Cowey 2000).

MRI STUDIES OF BRAIN DEVELOPMENT

Brain weight reaches adult values (about 1.45 kg) between 10 and 12 years of age. The fastest growth occurs during the first three years of life so that by the age of 5 years the infant's brain weighs about 90% of the adult value (Dekaban 1978). Clearly, changes in brain morphology in childhood and adolescence are more subtle than those in the first four years of life (see Paus et al. 2001 for a review of MR studies carried out during infancy). Visual evaluation of MR images is of little value at this point and the ability to obtain quantitative measurements is of the essence if we are to detect brain maturation during this "late" period of brain development. Several approaches have been used to obtain such measurements, including: (1) semi-automatic or automatic classification of brain tissue and subsequent "count" of image elements classified as a particular tissue type (e.g. white matter); (2) manual outlining of a structure of interest (e.g. the corpus callosum) on an MR image and the subsequent calculation of its volume/area; (3) voxel-wise analysis of local growth using deformation fields; and (4) voxel-wise statistical analysis of white or grey matter "density".

Based on a number of studies of typically developing children and adolescents (reviewed in Paus et al. 2001, Paus 2005), we can reach two conclusions. First, there is ample evidence that white matter continues to mature during childhood and adolescence, increasing its volume and becoming more myelinated. Second,

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the amount of cortical grey-matter changes in a non-linear fashion across different regions throughout childhood and adolescence. The most striking finding is the apparent 'loss' of grey matter during late adolescence, perhaps after the onset of puberty; the dorsolateral prefrontal cortex and the posterior part of the superior temporal gyrus appear to 'lose' grey matter the last (Gogtay et al. 2004). As discussed elsewhere, however, such changes in cortical grey-matter may represent a gain of tissue, namely an increase in intra-cortical myelination, rather than loss of grey matter (Paus 2005).

BRAIN MAPPING STUDIES OF AGGRESSION

Most of the literature on the neural underpinnings of aggressive behaviour reflects a theoretical framework that views aggression in the context of antisocial behaviour, such as violence and delinquency, rather than as one of the essential (adaptive) motivational states, such as hunger or maternal instinct (for recent criticism, see Tremblay 2003). It is therefore not surprising that the vast majority of previous studies are based on two methodological approaches: (1) clinical studies of overt aggressive behaviour in patients with brain lesions; and (2) neuroimaging studies of brain abnormalities in individuals who had committed acts incompatible with societal norms, such as murderers. I shall first review this literature and, given its emphasis on the frontal lobes, I will also provide a brief synopsis of the structure and function of this part of the primate cerebral cortex. In the second part, I will suggest an alternative approach for studying aggression and its elements in healthy subjects; this approach is based on a theoretical framework that views aggression as a social interaction between familiar individuals and, consequently, includes conflict resolution (reconciliation) as an integral part of aggressive behaviour (de Waal 2000).

Clinical observations. In the 19th century, several reports described individuals who had an injury to the frontal lobes and, subsequently, showed changes in their "personality" (Harlow 1868, Damasio et al. 1994). In the 20th century, several studies of war veterans confirmed a link between lesions to frontal lobes and an increased risk of aggressive behaviour (e.g., Kleist – cited in Brower and Price 2001, Lishman 1968, Virkkunen et al. 1976, Grafman et al. 1996; reviewed in Brower and Price 2001). The Vietnam Head Injury Study found a similar association between aggressive behaviour and lesions in the orbital and medial aspects of the frontal lobes (Grafman et al. 1996) Together, these lesion studies suggest that intact frontal cortex is important for adequate control of aggressive behaviour in adulthood. In the majority of these studies, the injury occurred in young male adults who had been studied many years later. Several case studies also described a high incidence of aggressive behaviour in adults who suffered lesions to the frontal cortex early (before the age of 8 years) in their lives (Price et al. 1990, Eslinger et al. 1992, Anderson et al. 1999). Together, these lesion studies suggest that intact frontal cortex is important for adequate control of aggressive behaviour in adulthood; the early-lesion cases suggest that remaining brain structures cannot compensate for the loss of brain tissue in childhood. Which parts of the frontal lobes are critical in this respect? A reconstruction of the skull injury suffered by Phineas Gage led Damasio and colleagues

to conclude that "the lesion...favored the ventromedial region of both frontal lobes while sparing the dorsolateral" (Damasio et al. 1994). The Vietnam Head Injury Study found a similar association between aggressive behaviour and lesions in the orbital and medial aspects of the frontal lobes (Grafman et al. 1996). To understand the significance of this pattern, let me briefly review the organization of the primate frontal cortex.

Frontal cortex. The frontal cortex constitutes about 35% of all cerebral cortex in humans and great apes (Semendeferi et al. 2002). It contains the primary motor cortex, premotor cortex (dorsal and ventral premotor cortex on the lateral convexity; supplementary motor area [SMA] and the cingulate motor areas [CMA] on the medial convexity) and the prefrontal cortex. The prefrontal cortex is further subdivided into the mid-dorsolateral and mid-ventrolateral frontal cortex, fronto-polar cortex, orbitofrontal cortex, and the mesial frontal cortex; the latter includes also the cingulate cortex surrounding the anterior part of the corpus callosum. Given the structural heterogeneity of the frontal cortex and the presence of extensive connectivity of fronto-cortical regions with other parts of the cerebral cortex, most prominently with the temporal and parietal cortex, it is not surprising that the frontal cortex supports a multitude of motor, sensory and cognitive functions. For example, the premotor areas on the medial convexity may be essential for sequencing behaviour (SMA) and willed initiation and suppression of movement (CMA; reviewed in Paus 2001). The mid-dorsolateral and mid-ventrolateral frontal cortex play an important role in working memory and retrieval, respectively (Petrides 1996). Maturation of the mid-dorsolateral frontal cortex underlies emergence of working memory during infancy (e.g. A-not-B test), and a further increase in working memory and planning during childhood. Maturations of the lateral prefrontal and/or cingulate cortices may be critical for the dramatic increase in the child's ability to suppress external interference observed just before the onset of puberty (e.g. suppression of reflexive eye-movements; Paus et al. 1990, Munoz et al. 1998; reviewed in Paus 2005). Age-related increases in the fMRI signal have been observed in the prefrontal and parietal cortex during the performance of a variety of tasks involving some form of response inhibition, including the Stroop task (Adelman et al. 2002), anti-saccade task (Luna et al. 2001), the Stop task (Rubia et al. 2000) and, to a certain extent, during the performance of a go/no-go task (Tamm et al. 2002; Bunge et al. 2002) and the Eriksen flanker task (Bunge et al. 2002). Maturation of the orbitofrontal, medio-frontal and cingulate cortex may be associated with the development of delayed gratification and other aspects of intentional behaviour, including the control of motivation states such as aggression. Underlying the latter one are extensive connections between the orbitofrontal/cingulate cortex and the amygdala (Barbas 1995, Morecraft and van Hoesen 1998).

Neuroimaging of individuals with anti-social behaviour. The second "classical" approach to studies of the neural underpinnings of aggressive behaviour is that of imaging the brains of individuals who show different forms of violent or antisocial behaviour; unlike the neurological patients described above, these individuals have not suffered any known external damage to their brains. Using structural MR imaging, two

studies described reductions of the volume of grey matter in different parts of the frontal lobes in aggressive patients with temporal-lobe epilepsy (Woermann et al. 2000) and individuals with antisocial personality disorder (Raine et al. 2000). The latter study described a 11 % reduction in the volume of the orbitofrontal cortex in 21 community volunteers with antisocial personality; like changes were not found in two different control groups. Using functional imaging, Raine et al. (1997) described hypometabolism in the prefrontal cortex in 41 individuals charged with murder or manslaughter; in subsequent re-analyses of this sample, Raine and colleagues found that this hypometabolism was present only in those individuals who did not have history of psychosocial deprivation (Raine et al. 1998a) and those who committed impulsive/emotional rather than purposeful aggression (Raine et al. 1998b). Similar findings were obtained in other clinical populations (reviewed in Brower and Price 2001).

Neurodevelopment and aggression. Given the above lesion and imaging findings, we may ask: What is happening in the human brain during early infancy and childhood that “enables” aggressive behaviour, which arguably peaks between two and four years of age (Tremblay, 2003; Tremblay et al., in press), and then provides adaptive mechanisms allowing its expression and resolution in a socially acceptable manner? It is clear that the most dramatic phase of brain growth takes place during the first two years of life: brain weight more than doubles, the overall volume of white matter and the degree of myelination increases sharply, with the overall increases in grey matter being less dramatic (e.g. Utsunomia et al. 1999, Matsuzwa et al. 2001, Paus et al. 2001). Importantly, some interesting regional differences are beginning to emerge. For example, the volume of grey matter constituting the hippocampal formation shows fast increase during the first two years of life and continues to increase slowly during childhood and adolescence (Utsunomyia et al. 1999). On the other hand, the volume of prefrontal grey-matter appears to increase slowly until the age of 8 years, followed by rapid growth between 8 and 14 years (Kanemura et al. 2003). Although the above patterns are based on cross-sectional studies of a relatively small number of infants and children, they provide a preview of what we may learn from several large-scale MR-based developmental studies that are under way. To come back to our question, it is possible that the development of structures in the mesial temporal lobes, such as the hippocampus and amygdala, underlie the initial development of aggressive behaviour while the relatively late development of cortical regions, such as the prefrontal and the lateral temporal cortex and their interconnections with the mesial temporal-lobe structures, enables adaptive regulation of aggression in the social context. Let us now examine some of the processes, and their neural substrate, that may be important for the latter.

Aggression and social cognition. Most acts of aggression take place in the context of social interactions among familiar individuals, be it at home, daycare, school or the workplace. As with any other forms of communication, each side of the conflict emits and receives a number of cues, both verbal and non-verbal, that are essential components of the overall dynamics of their (aggressive) interaction. I suggest that the study of the neural

substrates of such interactions, and their normal development, will benefit from the use of the experimental paradigms utilized over the past decade by cognitive neuroscientists interested in the brain mechanisms of inter-personal communication carried by gaze, face, body and voice. Over the past several years, a number of brain-mapping studies carried out with PET, fMRI and EEG identified a key set of brain regions involved in the processing of “biological motion” generated by the movements of the eyes, mouth and body. In such studies, the subjects view stimuli such as eye and mouth movements (e.g. Puce et al. 1998), hand movements/actions (e.g. Decety et al. 1997, Grezes et al. 1999; Beauchamp et al. 2002), or body movements conveyed by point-lights attached to the body (e.g. Bonda et al. 1996). Among other brain regions, biological motion leads consistently to the increases in neural activity along the superior temporal sulcus, STS (reviewed in Allison et al. 2000); the exact location may depend on the moving body part (e.g. mouth vs. eyes vs. hands) and the source of movement (tool vs. hand; Beauchamp et al. 2002).

Although most of the previous studies of biological motion used emotionally “neutral” stimuli, several investigators observed changes in brain activity in structures involved in processing emotional salience (amygdala) or reward value (orbitofrontal cortex). As suggested by Allison et al. (2000), feedforward and feedback interactions between the STS and amygdala may be critical for the discrimination of various facial expressions and for the attentional enhancement of the neural response to socially salient stimuli. Consistent with such an “amplification” mechanism, Kilts et al. (2003) observed significantly stronger neural response to dynamic, as compared with static, facial expressions of anger in both the STS and amygdala. Developmentally, the basic aspects of face perception are in place shortly after birth (Goren et al. 1975) but both the quantity and quality of face processing continues to increase all the way through adolescence (e.g. Carey 1992, Taylor et al. 1999, McGivern et al. 2002); perhaps, one of the structural correlates of such continuing maturation of face processing in an increase in white-matter density along the occipito-temporal pathway (Watkins et al. 2002).

Seeing and hearing signals of upcoming aggression is often enough to prevent it; in the monkey, this can be achieved by quickly averting gaze (e.g. Capitanio 2002). The frontal cortex and its various subregions (see above) are likely involved in evaluating the overall context and significance of the detected visual (eyes, face) and auditory (vocalization) displays of aggression and in generating the appropriate behavioural response. This response could, nonetheless, be an aggressive act. If this is the case, what happens next? In many primate species, aggression is often followed by “reconciliation” or “conflict resolution” (Aureli and de Waal 2000). Rather than viewing aggression as serving a “spacing” function, de Waal argues that “individuals try to “undo” the social damage inflicted by aggression, hence, they will actively seek contact, specifically with former opponents” (de Waal 2000). Several studies are beginning to document different forms of reconciliatory behaviour in children observed in naturalistic settings (e.g. Ljungberg et al. 1999).

Overall, careful studies of the neural substrate underlying

various aggression-relevant elements of social cognition will undoubtedly further our understanding of human aggression, its normal development and its socially unacceptable expressions.

CONCLUSIONS

Structural and functional neuroimaging is making strides in elucidating the structure-function relationships underlying aggression, as well as providing novel information on brain maturation in children and adolescents. Previous research has focused on studies of adult individuals and overt aggressive behaviour; lesions to the frontal lobes seem to increase the incidence of certain elements of aggressive behaviour, while having aggression-relevant behavioural traits appears to correlate with functional or structural abnormalities in this brain region. Very little is known, however, about the relationship between aggression and the individual's ability to detect and interpret non-verbal cues carried by the gaze, face and the body in social context. I suggest that the study of brain-behaviour relationships in this domain would be very helpful when combined, for example, with a detailed assessment of the perceptual and cognitive skills of individuals with different developmental histories of aggressive behaviour. It is also likely that future research on the role of the frontal lobes in aggression will shift from studying the actual act of aggression to investigating the brain substrate of reconciliation and conflict resolution. Finally, the use of structural and, perhaps, functional MR to define neural phenotypes underlying aggressive behaviour will facilitate our understanding of the interaction between the child's environment and his/hers genes; for example, which brain regions show structural differences in the young individuals with anti-social behaviour who presented with a particular polymorphism in the gene encoding monoamine oxidase A and suffered maltreatment during childhood (Caspi et al. 2002)?

While neuroimaging is a valuable tool in this endeavour, one should not forget about its limitations. For example, although T1-weighted MR images provide an impressive contrast between the (cortical) grey and white matter, we are not sure about the biological source of signal differences between various clinical or age groups; many factors may influence the signal, including the density of neurons, glia or vascularization, or the degree of (intracortical) myelination. Functional imaging poses different challenges; for example, are age-related differences in the fMRI signal the cause or consequence of age-related changes in a given behaviour? In other words, how do we make sure that the "stimulus" is held constant across different populations so that we can evaluate the magnitude of neural response to the same probe rather than use the fMRI signal as a mere correlate of different behaviour? Finally, structure-function correlations observed with structural and functional neuroimaging are just that, correlations. Other experimental approaches must be used to confirm whether or not a given region is necessary for a given behaviour; such an inference can only be made when irreversible (lesion) or reversible (electrical or pharmacological stimulation) manipulations lead to the predicted behavioural consequences. Although some of these techniques can be used in (adult) human subjects, the ultimate tests would require animal models.

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