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Review

Novel insights from quantitative imaging of the developing cerebellum

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SUMMARY

There is increasing evidence that points to the central role of the cerebellum in many areas of human behaviour – in health and in illness. The findings reviewed here shed further light on the developmental vulnerability of cerebellar cell types, and highlight the new imaging techniques being used in this research. This article reviews some new advances in our understanding of the normal cerebellar growth trajectory, and how this may become disturbed by pathological processes. Cerebellar development is now being implicated in many conditions, from autism and other neuropsychiatric disorders to diabetes.

1. Introduction

The traditional neurological view of the cerebellum as part of the motor system has been progressively challenged over the last two decades. It is now clear that the cerebellum has reciprocal anatomical connections that link it not only to motor areas, but also to frontal, parietal and limbic areas of the cortex [1] – the areas where interesting and characteristically human attributes and abilities are localized. It seems likely that the majority of the human cerebellum is connected to the "association" cortex [2]. Recent neuroimaging work has confirmed and refined this idea. Riedel et al. [3] performed a meta-analysis of data collected as part of the BrainMap project, with the aim of identifying cerebellar structures that co-activate with the cerebral cortex. They concluded that the cerebellum is involved in a wide variety of areas of thought and behaviour – including cognition, emotion, perception, and interoception – as well as action. The cerebellum's repeated structure has led to the idea that it perhaps performs a mathematically similar kind of operation on inputs from different brain areas. Cerebellar lesions are associated with mental health and neuropsychological problems – termed the "cerebellar cognitive affective syndrome" by Jeremy Schmahmann et al. [4]. This syndrome comprises impairments of language, visuospatial memory and executive function. The lateral lobes of the cerebellum and their reciprocal connections to the cerebral cortex are greatly expanded in humans compared to other primates [5].

The next crucial step towards a full understanding of the cerebellum is to discover how the cerebellum grows and develops, as well as identifying the complications of maldevelopment. The cerebellum has a different developmental sequence from the cerebral cortex, but like the cerebrum it has cell populations that have particular vulnerabilities at different times in development. This is itself of great clinical interest; for example, several neuropsychiatric disorders that have their origins in neurodevelopment – such as autism and schizophrenia – also include cerebellar pathology in their phenotype. A good understanding of cerebellar growth and development will be crucial in unravelling these illnesses, which represent a huge burden of illness worldwide. Our understanding of the brain and behaviour is severely limited if we do not factor in how they change over time. New insights have widely established how magnetic resonance imaging (MRI) has recently revolutionized our understanding of neurodevelopment across the human lifespan. This chapter will highlight some of the quantitative MRI techniques that are used so productively to elucidate the development of the cerebrum and which are now being applied to the cerebellum.

2. What neuroimaging tells us about normative cerebellar development

One of the key tasks in understanding neurodevelopment is establishing normative growth trajectories. There are two broad neuroimaging approaches to this. The first, which is often more

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feasible to perform, is to look at the structure in question, measure it, and make correlations between that measurement and the subject's chronological age. This is a "cross-sectional" or correlational approach, and can be very useful. It can be used postmortem, for example, to examine tissues in great detail. The advent of non-destructive, in-vivo imaging methods makes it possible to have a truly developmental study. In this paradigm, the structure under investigation can be measured several times, ideally during interesting periods of development. Using a longitudinal study, any changes over time can be directly assessed. Both cross-sectional and longitudinal studies will be highlighted here. Indeed, some groups have combined the two approaches of cross-sectional and longitudinal studies using instead mixed-model statistics [6]. I will start by looking at recent insights into very early development of the cerebellum and then consider its development to adolescence, and into early adulthood.

2.1. In utero and in infancy

The primary output cells of the cerebellum – the Purkinje cells – and their output nuclei (the dentate, emboliform and globose nuclei) develop relatively early in gestation. However, the granule cells (excitatory; the source of parallel fibres) appear later. They are actively migrating into position during the third trimester of human development [7]. Cerebellar granule cells are possibly the most numerous cell type in the nervous system. During the third trimester they are likely to be vulnerable to a variety of potential environmental and situational toxins including hypoxia [8] and steroid treatment [9,10]. Other cerebellar cell populations would likely be affected too, as their cells lost the expected trophic and signal-dependent interactions with cells from affected areas. The reciprocal connections between the cerebellum and the cerebrum indicate that primary cerebellar lesions may affect brain development in different sites (and conversely, cerebral lesions affect cerebellar growth and function by long-range trophic interactions). This is known as "crossed cerebellar diaschisis" [11].

The very earliest stages of cerebellar development have been mapped (from 18 weeks of gestation) using structural MRI [12]. This study revealed that the rate of cerebellar growth reaches a sevenfold enlargement between 20 and 31 weeks' gestation. This trend continues postnatally, during the first year after birth, in which the cerebral cortex doubles in size, while the cerebellum more than triples. The growth of cerebellum continues to outstrip that of the cerebrum as development progresses into childhood [13]. In general, just as in the cerebrum, the phylogenetically older parts of the cerebellum develop before the neocerebellum, the development of which appears to be protracted [14].

Some recent studies have directly addressed cerebellar development using a longitudinal methodology. Scott et al. [15] analysed three-dimensional MRI scans of fetal brains, and extracted information about volume, dimensions and surface curvature. They used these data to look at growth rates from 20 to 31 gestational weeks. They found that cerebellar growth is exponential rather than linear during this time period.

Higher field strength magnets can make MRI images more detailed. Liu et al. [16] have used 7T structural MRI in human fetuses from 14 to 22 gestational weeks, postmortem. In their cross-sectional study, they obtained detailed images of the cerebellum, suggesting a growth curve for cerebellar volume and identifying transverse cerebellar diameter for the second trimester.

Another active developmental process is myelination. T2-weighted fetal MRI scans have been used to provide a proxy measure of myelination (myelin is less intense on T2-weighted images). Using this technique, Triulzi et al. [12] showed that myelination of the cerebellum proceeds in a caudal–cranial direction. At 30–31 gestational weeks, the inferior and superior cerebellar peduncles and flocculonodular lobe are undergoing myelination, but the middle cerebellar peduncles (containing cortico-ponto-cerebellar connections) are not yet myelinating. By term, the dentate nuclei are myelinating, along with the decussation of the superior cerebellar peduncles. After birth, there is rapid myelination that includes the middle cerebellar peduncles by around the fourth month of life [17].

2.2. Childhood, adolescence, and beyond

Tiemeier et al. [18] performed structural MRI longitudinally (repeated measurements in the same individuals) to examine changes in the cerebellum in healthy volunteers aged between 5 and 24 years. To analyse the images they used a combination of automated and manual methods. Each participant was scanned three times, at intervals of two years. Total cerebellar volume followed an inverted "U" trajectory, revealing sexual dimorphism – with cerebellar volume peaking at around 12 years in females and 16 in males. This parallels sex differences in the timing of peak cortical gray matter, which have been extensively reported [6]. Weirenga et al. [19] have also found an inverted "U" trajectory of cerebellar development using repeated MRI scans, analysed using the Freesurfer package. Study participants ranged in age between 7 and 24 years. The cerebellar growth trajectory was quite different to those of other subcortical structures – the caudate, putamen, and nucleus accumbens all decreased in volume with age. Tiemeier et al. [18] also found that anatomical subdivisions of the cerebellum had different developmental trajectories. Interestingly, the phylogenetically most recent parts mature relatively late. Again, this is consistent with what is known about the maturation of the cerebral cortex. This is also very consistent with the theory elaborated by Leiner et al. [5] that there has been a phylogenetic expansion in cerebellar areas that connect to association cortex.

Bernard et al. [20] performed quantitative structural (s)MRI of the cerebellum in individuals from adolescence to adulthood (12–65 years). This was not a truly longitudinal study, but the authors did examine cognitive tasks in relation to cerebellar volume. This study found another "inverted U," or quadratic, relationship between posterior cerebellar volume and age. Other regions such as the anterior cerebellum and vermis had different patterns in relation to age.

Expanding upon the volumetric imaging studies, Bernard et al. [21] further examined how the functional and structural connectivity of the cerebellum changes during the crucial transition from adolescence to adulthood. Measuring for both structural and functional connectivity, Bernard et al. used resting-state fMRI (functional connectivity MRI) to assess functional connectivity and DTI to image white matter and assess cerebello-thalamo-cortical structural connectivity. In a longitudinal study, 23 people, aged from 12 to 21 years, were imaged once, and then again one year later. Functional connectivity of Crus I and Crus II decreased over 12 months. These changes were correlated with increased white matter structural integrity (indexed by fractional anisotropy: FA) in the cerebello-thalamo-cortical tract. This is consistent with the known developmental trajectory of cerebral gray matter and white matter, mainly that there is protracted development of lateral cerebellar networks and their long-distance white matter connections. These areas are the cerebellar regions linked to "association" cortex, which is also known to have a protracted developmental course compared to sensorimotor cortex [6]. These studies suggest that the reduction in functional connectivity observed is due to resting state networks being refined ("pruned") over time, in order to increase efficiency. Synaptic pruning and myelination are plausible underlying mechanisms.