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Brain Maturation – It covers three decades: Considerations of the Development of ADHD

As children grow, parents and teachers alike wonder at the skills the young develop – physical and cognitive abilities alike. By the age of 5 years the child's brain is packed with far more neurons (grey matter) that make far more connections than in the adult brain. Over the next 10 years these walking, talking interactive wonders must then cope with conflicting stimuli and signs from the events around them. They must learn, fast and well. They must also be capable of switching and maintaining attention, able to plan behaviour, develop goals, construct, hold and recall concepts – put them in to effect and be able to communicate about them.

Is it really not surprising that the hugely complex biology underlying this development sometimes takes an inefficient course? Delays may occur and inappropriate connections be made. Precisely over this long haul from the first to the second decade of

life the process of reducing grey matter for efficiency and establishing the right pattern of neuronal connections can take an anomalous course. One such case gives rise to the neurodevelopmental condition known as attention-deficit/hyperactivity disorder (ADHD). Here, the maturation of those abilities I have listed above follows a different course from 5 to 15 years of age – and we are now in a position to show that this developmental course in the biological bases for behaviour and what may go wrong with it, may even go on quite some time after the age of 25 years.

We can illustrate this by taking a biological marker of a fundamental cognitive ability, – that of detecting a deviant sound in a series of otherwise similar auditory stimuli. A recording of electrical brain activity from the skull (electroencephalogram, EEG) after a few hundred tones – when averaged with respect to the sound's onset – shows a distinctive negative-going, excitatory event-related potential (the ERP). A subtraction of the ERP following a common repeated standard tone from that after a rare, perhaps deeper deviant sound gives us the mismatch negativity (MMN). We all develop deviance detection as infants: it is automatic and occurs without the need to consciously listen. But, note that if this early stage of information processing goes wrong, one can hardly expect successive 'higher' abilities that build on it to be accurate.

There is no need to worry. Children with ADHD develop a similar and a normally sized MMN as rapidly as those without ADHD. Curiously, if we record from an array of sites over the skull of 10 year-olds, we note from the topography that this ability develops first over the right

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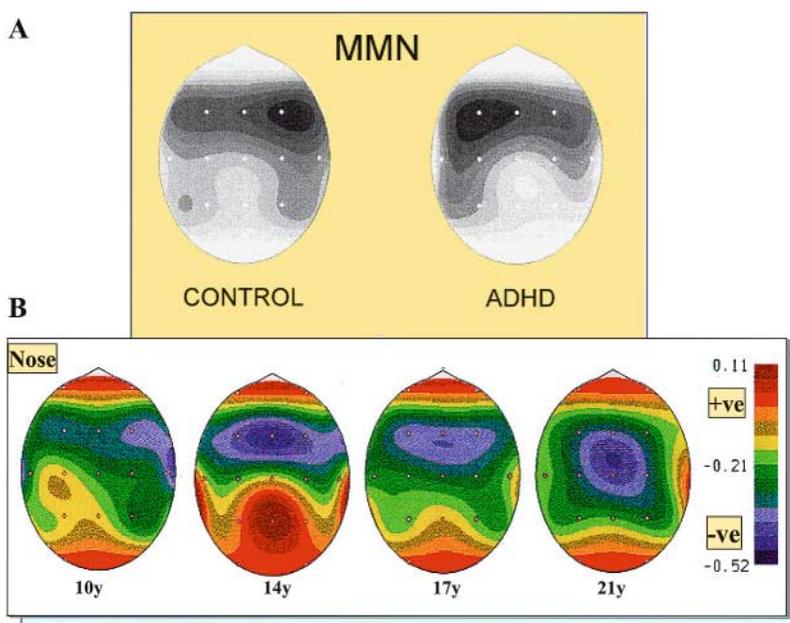


Figure 1. Both parts A and B show the topographical distribution of negative potentials (MMN) representing the detection of deviant sounds on a model of the skull with the nose pointing up the diagram. Part A shows normal right hemispheric development in 10 year-old children side by side with anomalous left hemisphere development in 10 year-old children with ADHD (Oades et al., 1996). Part B shows the normal development of MMN topography (blue colour) over the skull for groups of 10, 14, 17 and 21 year-olds (Oades et al., 1997). Bilateral representations typical of young adults are achieved post-pubertally, and their latencies mature at about 17 years of age (not shown).

hemisphere, before it becomes bilaterally distributed after puberty. But in those with ADHD it is first evident on the left side (Oades et al., 1996, Figure 1). This appears to reflect a right frontal impairment. Its compensation, however, may also compromise abilities that would normally otherwise develop in an uncomplicated way on the left (e.g. language related functions). More recent neuroimaging studies confirm impaired patterns of brain activation in the right hemisphere while children with ADHD meet more demanding cognitive challenges (e.g. stop- and delay-tasks, Rubia et al., 1999). Thus, there is evidence for a major ‘dislocation’ in the pre-pubertal development of the anatomical bases underlying selective information processing: it is one that affects the efficient division of labour between right hemisphere function in sensory, spatial, holistic processing and the left hemisphere involvement in fine detailed analyses, working memories and language.

After puberty the wave of development, cutting down on excess grey-matter and pruning back of the number of synaptic connections, progresses forward over the ever more frontal parts of the brain (Gogtay et al., 2004). These parts, among other functions, harbour the ability to switch the direction of processing (should the deviant sound be interesting, threatening or aversive). MMN latencies that reflect the speed and efficiency of processing, mature in the late teens (Oades et al., 1997). Is development then all over?

We have been using an algorithm known as “brain electrical source analysis” (BESA) to calculate where the sources must be in the brain to

account for the activity we record. It is not surprising that two such sources are located in the left and right auditory cortices – the highest centres receiving sensory perceptual information. More intriguing is the location of others in the posterior end of the anterior cingulate cortex near the midline, and in the anterior inferior frontal cortex on the right (Jemel et al., 2002). A comparison of 30 year olds with 17 year olds showed that the sources in the auditory cortices (temporal lobe) moved 10–15 mm sideways and down during the third decade of life. Those in the frontal lobes travelled by a similar amount further posterior at the back end of the forebrain (the cingulate) or further anterior at the front end of the forebrain (the inferior-frontal: Wild-Wall et al., 2005). It now seems that the brain is going on developing way past the age of consent and achievement of majority (Figure 2). Indeed, the achievement of adulthood is not so fixed as popular law and lore would have it.

There are several reasons why this has significance for studying what underlies ADHD. The first is methodological. To study what happens differently for ADHD subjects from mid-adolescence to “30 year-old adulthood” researchers must precisely match their healthy comparison subjects for age. It is no longer sufficient to contrast, say, a comparison group of 30 healthy subjects with a mean age of 25 years when the individuals’ age range from 19 to 32 years, with a study group whose mean age of 25 years was made up of subjects aged 24–26 years. The second reason is that we now have grounds to predict that the ‘maturation lag’, previously postulated to account for some of the problems in childhood ADHD, may indeed emerge in the more recently recognised adult form of ADHD. About a third of 8–12 year-old children with ADHD show a ‘maturation lag’ in the pattern of EEG oscillations recorded: (this includes

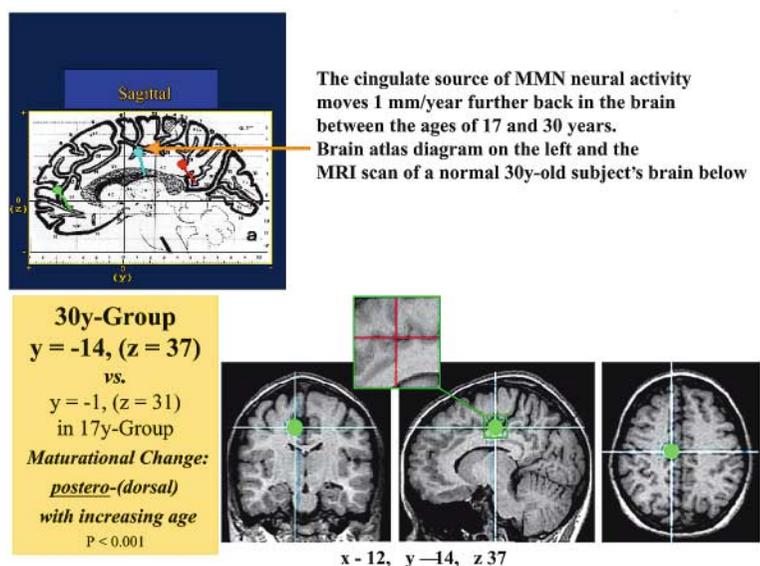


Figure 2. The top part shows 3 of the 4 dipole sources of activity generating MMN placed on a diagram taken from a neurological atlas of brain structures as viewed from the left hand side (the front end is on the left). (Green = inferior/mid frontal, turquoise = midline cingulate, red = auditory cortex in the temporal lobe: Jemel et al., 2002). The bottom part shows the cingulate source (mean solution for a group of normal 30 year-olds) placed on an MR image of one of these subjects, which lies 1.3 cm, on average, further back along the anterior-posterior y-axis than in a group of normal 17 year-olds (Wild-Wall et al., 2005). [The z-axis represents the more vertical, dorso-ventral axis.]

an increased frontal and decreased posterior total power in the recording, Clarke et al., 2002). Remarkably, at least a third of those with a childhood diagnosis of ADHD retain some of their difficulties into adulthood (Faraone et al., 2000). We do not yet know if these data refer to the same type of subject. However, a recent study of 28 year-olds who had and have such difficulties described cingulate dipoles for the mismatch between ‘go’ (respond) and ‘no-go’ (withhold response) stimuli (Fallgatter et al., 2005). These sources of activity also differed on the anterior-posterior Y-axis in comparison with other people without ADHD problems. Their patients’ dipole-sources were further anterior – like those we have also shown to reflect earlier stages of maturation.

In summary, we can calculate and illustrate the location of sources of activity of the brain underlying a fundamental cognitive activity (auditory deviance detection, MMN) in two and three dimensions. This marker shows that (at least) two sorts of anomaly in normal brain development occur as a child with ADHD grows up. The first is specific to pre-pubertal development and reflects the differential roles of the two hemispheres of the forebrain. The second is the maturational lag in brain expansion (rostrally-caudally in the frontal and laterally in the temporal lobes) that may become evident from puberty, but potentially dominates in the adult forms of ADHD. As a precautionary note, it should be remarked that this latter feature relates to neurodevelopment – it may not be specific to ADHD, but be a feature accompanying some (but not all) other neurodevelopmental disorders. We have indications that some lag may also be evident in psychoses with an early onset in adolescence (Oknina et al., 2005).

The jury is still out on whether these features reflect the expression/non-expression of certain genes at certain stages of growing up, or on the extent to which these processes may prove sensitive to drug or other treatments. The indications are that currently typical medication directed towards catecholaminergic transmission may not interfere with the development I have described, although the expression of the source activity may be modestly facilitated. Such questions demand and are receiving close attention.

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