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The maturation of mismatch negativity networks in normal adolescence

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HIGHLIGHTS

- We investigated the neurophysiological mechanisms underpinning the generation of the mismatch negativity (MMN) in adolescence using dynamic causal modelling (DCM).
- We found that cortical regions in the temporal and frontal lobes, involved in auditory processing, mature with increasing fronto-temporal connectivity together with increased sensitivity in the temporal regions for changes in sound stimuli.
- This study may offer an explanation for the neurobiological maturational changes of the MMN in the adolescent brain.

ABSTRACT

Objective: We investigated the neurophysiological mechanisms underpinning the generation of the mismatch negativity (MMN) and its development from adolescence to early adulthood.
Methods: We used dynamic causal modelling (DCM) to study connectivity models for healthy adults and adolescents. MMN was elicited with an auditory oddball paradigm in two groups of healthy subjects with mean age 14 ($n = 52$) and 26 ($n = 26$). We tested models with different hierarchical complexities including up to five cortical nodes.
Results: We showed that the network generating MMN consisted of 5 nodes that could modulate all intra- and internodal connections. The inversion of this model showed that adolescents had reduced backward connection from rIFG to rSTG ($p < 0.04$) together with increased excitatory activity in rSTG ($p < 0.02$). There was a reduced modulation of excitability in rSTG ($p < 0.02$) and of forward connectivity from lA1 to lSTG ($p < 0.03$).
Conclusion: The cortical network generating MMN continues to develop in adolescence up to adulthood. Cortical regions in the temporal and frontal lobes, involved in auditory processing, mature with increasing fronto-temporal connectivity together with increased sensitivity in the temporal regions for changes in sound stimuli.
Significance: This study may offer an explanation for the neurobiological maturation of the MMN in adolescence.

1. Introduction

The human brain continues to develop into late adolescence. This includes several important brain maturational changes such as synaptic pruning and reorganization, programmed cell death, and dendritic/axonal arborisation (Changeux and Danchin, 1976; Rubia et al., 2006). The total grey matter tissue undergoes a slow decrease during adolescence together with an increase in white matter tissue in mainly associative cortical regions in the parietal, temporal and prefrontal regions (Casey et al., 2000; Gomes et al., 1999; Gogtay et al., 2004; Rubia et al., 2006; Sowell et al., 2004). Studying the physiological changes of cortical networks during adolescence should increase the understanding of how the adolescent brain develops and evolves into adulthood.

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The difference in auditory event related potentials (ERP) elicited by novel, or odd-ball, events embedded in a stream of repeated stimuli produce a distinct response, the mismatch negativity (MMN) (Näätänen et al., 2001). MMN has been used to give clinical information for a multitude of medical conditions (Näätänen et al., 2012). It has been used to index excitability in epilepsy (Miyajima et al., 2011) and schizophrenia (Banati and Hickie, 2009), level of consciousness in coma (Naccache et al., 2005) and persistent vegetative states (Wijnen et al., 2007). Advanced analysis of MMN using dynamic causal modelling (DCM) has been performed on patients in a vegetative state showing impaired top-down modulation (Boly et al., 2011). MMN has been shown to be relatively stable from early childhood until adulthood and can be elicited with frequency deviants (Cheour et al., 2000). However, developmental changes in amplitude and latency of the MMN as well as other ERP components have been described in some but not all studies (Bishop et al., 2011; Wild-Wall et al., 2005; Wetzel et al., 2006). The conflicting results have been partly suggested to be due to the fact that different measures have been used in different studies to analyse the MMN (Bishop et al., 2011). Several studies have also shown a change in topography in the event-related potentials and MMN with development (Cheour et al., 2000, Martin et al., 2003, Maurer et al., 2003, Wild-Wall et al., 2005). In adults two generators have been described, a temporal and frontal generator, and it has been further suggested that these develop at different rates (Cheour et al., 2000; Gomot et al., 2000; Gumenyuk et al., 2003). The above suggests that the MMN undergoes a quite complex development during adolescence where a single or a few characteristic features of the waveform (like amplitude or latency) might not be able capture or even detect the changes occurring, perhaps partly explaining the conflicting results for adolescents uncovered by different studies. Uncovering the physiological changes in MMN generation during adolescence using DCM might shed some light on the development of the waveform and also increase the understanding of the physiological changes expected in this age bracket where the brain undergoes its final maturation. A deeper understanding of the physiological changes in MMN in adolescence may help using MMN as a clinical marker for various disorders.

Several competing hypotheses have been put forward regarding the generation of the MMN, based on experimental results obtained by electric and magnetic evoked responses and functional magnetic resonance imaging (Garrido et al., 2009a). The model adjustment hypothesis states that the MMN is generated by a regularity violation in a structured auditory sequence (Näätänen et al., 1992). The deviant sensory input is compared with a memory trace of previous stimuli by a temporo-prefrontal network generating the ERP (Giard et al., 1990; Opitz et al., 2002; Doeller et al., 2003). The adaptation hypothesis however, claims the MMN to be generated by a neuronal adaptation (or habituation) in the auditory cortex. According to this view, the MMN is simply the difference in the N100 response to a novel sound compared to the suppressed and delayed N100 response caused by repeated stimuli (Jääskeläinen et al., 2004). Finally, the predictive coding hypothesis has been able to unify the two previously described theories. Predictive coding postulates that the brain is a hierarchically organised cortical system, in which each level strives to attain a compromise between sensory inputs and top-down predictions (Garrido et al., 2009a). The generation of the MMN has been framed within predictive coding as resulting from differences between predictions formulated in cortical areas involved in secondary processing of auditory input and the sensory inputs arising from cortical areas involved in the primary processing of the auditory input (Friston, 2005; Garrido et al., 2009b). The predictions formulated by cortical areas involved in secondary processing of auditory input due to stimulus repetition have been shown to induce reduction of the connectivity within and between cortical areas causing a decrease in the evoked response, a phenomenon known as repetition suppression. The theory provides a mechanism through which the generative cortical network can adapt (or habituate) to repetitive stimuli. (Garrido et al., 2009c). On presentation of the deviant tone the increased prediction error manifests itself as an increased evoked response resulting in the MMN.

Auditory sensory memory is related to adaptation in the auditory cortex during repeated presentation of the standard tone. However, during the development and maturation of the human brain, sensory memory has not been shown to change significantly after the preschool years. (Gomes et al., 1999). In contrast during adolescence there is an increase in white matter together with cortical thinning especially in associative cortical regions (Rubia et al., 2006; Casey et al., 2000; Giedd et al., 1999; Gogtay et al., 2004; Olesen et al., 2003). It is possible that these structural changes could affect the deep hierarchical levels of the cortical model generating the MMN. In this study we will investigate the structure of the hierarchical cortical network generating the MMN and investigate possible changes in this structure with development. However, it must be noted these changes might not correlate directly with cortical function (and implicitly behaviour) as changes in cortical structures of generating networks do not necessitate changes in function. More specifically, we will investigate changes in connectivity between the nodes of the generating network and the activity of the nodes themselves. At present we will be investigating changes in a cross-sectional study although a longitudinal study would be required to get more precise information of the maturation of the cortical network generating the MMN.

We used a classical oddball paradigm and Bayesian inference of DCMs to investigate the electrophysiological mechanisms underpinning the changes of the MMN in the maturing brain.

2. Methods

Below we provide a description of the methodology used. For further detail please refer to (Cooray et al., 2014).

2.1. Subjects

Two populations consisting of adolescents ($n = 52$, 15 males, mean age 14, range 10–18 years) and adults ($n = 26$, 12 males, mean age 26, range 20–35 years) were recruited for the study. The adults were recruited randomly from the Swedish population registry while the adolescents were recruited from a school in northern Stockholm. All subjects were asked about their medical history. Exclusion criteria for subjects to be recruited from the Swedish population registry were ongoing medication or previous disease or trauma that might have affected the brain and cognitive function. Subjects were asked the following questions before they were recruited: (1) Were you born prematurely or with a complicated labour?; (2) Reduced vision after optical correction?; (3) Reduced hearing?; (4) Unconscious due to traumatic injury?; (5) Have you, or ever had, the following disorders: (5a) stroke, cerebral embolism, haemorrhage; (5b) migraine; (5c) dyslexia; (5d) infection of the brain or nervous system; (5e) epilepsy; (5f) intracranial tumour; (5g) psychiatric disorder; (5h) addiction to alcohol or any other drugs; (5i) chronic disorders such as multiple sclerosis, Parkinson's disease, epilepsy, motor neuron disease or schizophrenia?; (6) Current medications. Note that participant hearing was not specifically examined; however, all subjects reported of normal hearing. All subjects and guardians, if subjects were under the age of 18, were informed about the nature and purpose of the study before consenting to participate. This protocol was approved by the human ethics committee of the Karolinska Institutet (ethical