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## Cognitive neuroscience: Theta network oscillations coordinate development of episodic memory

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**Our ability to remember life events matures through childhood and adolescence. A new study has revealed how theta oscillations between two anatomical brain regions supporting memory and executive functions are synchronized and develop across age through functional and structural connectivity.**

Our ability to remember people, scenes and episodes from particular life events emerges early on in young children. We can recall outstanding details of very remote memories going back to when we were just a few years old. When we visit the people and places that we grew up with, our memories become alive again with a compelling and deep sense of familiarity. This awe-inspiring ability to capture, store and recall the past improves as we mature into adolescence and adulthood; with age, more information can be remembered in a gradually extending scale of time and space. Elements of our memories can be associated together in a wider context of where and when they happened relative to each other. How this incredible maturation process is coordinated in the dynamics of the human brain electrophysiology has been elusive due to limited access to its direct recordings. A paper in this issue of

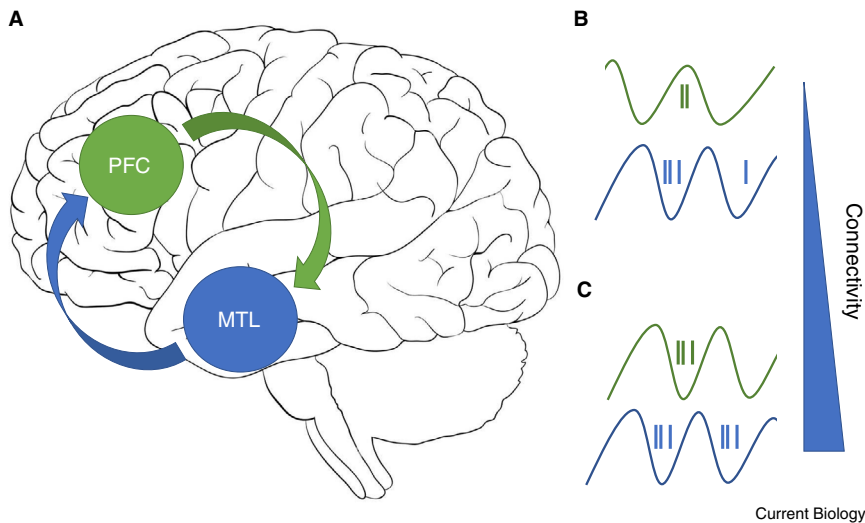
*Current Biology* by Johnson *et al.*<sup>1</sup> offers new insight into the way that this higher brain function develops during post-natal life.

By taking advantage of intracranial recordings in pediatric cases of intractable epilepsy, Johnson *et al.*<sup>1</sup> were able to measure electrophysiological activities engaged during remembering photographs of spatial scenes in children and adolescents (5–20 years old). They employed a classic task probing episodic memory — a type of declarative memory for particular events — where a series of previously viewed and new photographs were recognized as novel or old. Performance in this classic task is known to gradually improve with age as the critical brain regions and their connections develop. As the task was performed, intracranial electrocorticographic signals were recorded from special electrodes surgically implanted on the medial

temporal lobe (MTL) and on the prefrontal cortex (PFC).

These two limbic and cortical brain structures are known to play pivotal roles in episodic memory function, which is highly conserved in the evolution of the human brain. Electrophysiological studies in rodents have implicated hippocampal-prefrontal rhythmic interactions in coordinating communication for memory-based decisions<sup>2,3</sup>. Successful decisions guided by memory of previously visited spatial locations on a maze depend on coordinated oscillations of hippocampal and prefrontal neuronal populations in the so-called theta rhythmicity. Disrupting these cortical-limbic network oscillations pharmacologically impairs memory performance<sup>4</sup> and may even be important in our understanding of the diseases affecting the developing brain like schizophrenia<sup>5</sup>. Therefore, hippocampal-prefrontal theta interactions provide a tenable mechanism not only for





**Figure 1. Coordinated theta oscillations between MTL and PFC support development of memory formation.**

(A) During encoding of new images, synchronous theta oscillations increase probability of creating new memories. (B) Oscillations represent desynchronized theta rhythms and cell firing (vertical lines) between the color-coded structures at an early stage of brain development with little white matter connectivity and information transfer. (C) More developed white matter connectivity and synchronous theta coordination enhances information transfer and episodic memory function at late adolescence and adulthood.

communicating information about recent scenes or episodes but also for maturation of higher order cognitive functions at larger scales in brain development.

On the basis of these rodent and other animal and human studies, Johnson *et al.*<sup>1</sup> focused their investigation on the theta oscillations of the hippocampus in MTL and in the three anatomical subdivisions of PFC (inferior, middle and superior frontal gyrus), where intracranial surface grid and strip electrodes in these clinical cases are commonly implanted to localize seizures. They first excluded the electrode contacts with epileptic activities and focused their analysis on the majority of the remaining ones that showed clear physiological oscillations in the theta frequency range (2–8 Hz). In agreement with other human studies<sup>6</sup>, there were two distinct types of low and high theta oscillations centered at 3 and 7 Hz, respectively. The first interesting finding was that the center frequency decreased with age for the slower rhythm, and increased for the faster rhythm, in MTL and PFC. So, as the brain develops, the slow theta gets gradually slower and the fast theta gets faster.

Johnson *et al.*<sup>1</sup> next looked at the hippocampal–prefrontal interactions in

real-time of memory processing. It has been known that the power of theta oscillations in either of these structures (MTL or PFC) is indicative of successful memorization. Coordination of the theta rhythms across the brain structures was used to further resolve the strength and direction of communication in specific areas and times of memory processing. For example, the authors found significant amplitude coupling of the slow theta rhythms across the hippocampus and the inferior frontal gyrus after presentation of images for memory recognition. A significant lag between the two — with the cortical area leading the hippocampus — was found after the memory-based decision when images were rated. Fast theta rhythms in the same areas showed significantly more phase (not amplitude) coordination at similar times in the task. In general, the slow theta rhythm showed coordinated variation of the amplitude, whereas the fast rhythms revealed coordinated alignment of the phase that predicted memory performance.

The novel question posed by Johnson *et al.*<sup>1</sup> was: how do these theta interactions change across the brain development? In their previous study<sup>7</sup>, the authors found age-related differences in the dynamics of neural oscillations

within the maturing prefrontal cortex. Now, with the same patient tasks, they have associated the strength of coordination in the theta network oscillations between MTL and a specific PFC gyrus with brain development and memory performance. Synchrony of the amplitude in the slow and of the phase in the fast theta band was becoming stronger with age. Congruent with the age-related functional changes in the theta interactions, there was a parallel structural growth of the white matter connectivity between these limbic and cortical regions. The stronger the theta interactions, the denser the structural connections, which separated the high and low performers in the task.

The reported functional and structural changes in brain development provide an attractive neural mechanism for maturation of episodic memory function with age. It has been known that the prefrontal cortical connections develop until early adulthood and are pivotal for maturation of the declarative memory functions<sup>8,9</sup>. It is also known that theta oscillations play an important role in supporting the prefrontal cortical cognitive functions in the adult brain<sup>10</sup>. This study<sup>1</sup> now links the two lines of evidence in an elegant framework of synchronous hippocampal–prefrontal cortical activities and anatomical connections throughout brain development.

The framework leaves important gaps to be filled. For instance, how exactly synchrony between MTL and PFC would enhance memory formation? One of the possible mechanisms is that PFC and MTL coactivate basal ganglia nuclei, which in turn enhance long-term potentiation of the MTL–PFC synaptic connections via dopaminergic modulation<sup>11</sup>. Interestingly, coordination of neuronal firing in a dopaminergic nucleus, substantia nigra, with phase of the theta oscillations in PFC supports encoding of new memories<sup>12</sup>. Precise coordination of neuronal activities in theta rhythm could work by synchronizing cell assemblies across a network of remote areas to facilitate information transfer for successful encoding of new memories<sup>13</sup>. This in turn would lead to gradual enhancement of memory functions with development of structural connectivity (Figure 1).

More details about the neural mechanisms are now required to test the model framework. Although most of the prefrontal cortical electrode sites showed theta oscillations, the MTL–PFC interactions would almost certainly not engage the entire neuronal populations. Anatomical and spectral granularity in the Johnson *et al.*<sup>1</sup> study is limited. One would predict spectral activities in the higher frequency bands to be mapped onto more discrete cortical areas or domains<sup>14,15</sup>. Memory processing can be mapped and localized to specific cortical areas<sup>16,17</sup>. How theta oscillations modulate limbic-cortical activities of neuronal assemblies that support specific memory representations<sup>18</sup> remains to be established in humans. Theta oscillations are known to move in cortical space<sup>15,19</sup>; hence, a greater anatomical granularity of the reported interactions would provide fascinating insights into their dynamics at various stages of brain development.

Finally, a casual relationship between the reported network oscillations and episodic memory performance can be tested. Johnson *et al.*<sup>1</sup> based their conclusions on statistical correlation and modeling of interactions between the electrophysiological activities, structural changes, task performance and age. An intervention that specifically altered these measures would contribute more casual evidence. Direct electrical stimulation in specific cortical areas was shown to modulate cortical activities and performance in another episodic memory task<sup>20</sup>. Probing these mechanisms at larger scales of long-term memory and across development in the human brain may soon be possible with implanted devices for continuous recording and stimulation.

The Johnson *et al.*<sup>1</sup> paper opens new avenues for the role of theta interactions on a larger scale of space and time. If previously we have been thinking about neurons that ‘fire together and wire together’ in the theta rhythm supporting local memory formation and consolidation across seconds, days or

weeks, then now we can allegorically speak of global theta waves that ‘flow together and grow together’ as our brain network connections and their supported cognitive functions develop over our lifetime.

#### DECLARATION OF INTERESTS

The authors declare no competing interests.

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