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Review

Early functional brain development in autism and the promise of sleep fMRI

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ABSTRACT

Functional magnetic resonance imaging (fMRI) is a powerful tool for examining brain function but has yet to be systematically applied to the study of brain development in autism. Recently, however, scientists have begun to apply fMRI during natural sleep as a mechanism to study function in the developing brain. When considering the study of autism, this method opens considerable doors because it eliminates biases of past studies which only sampled from high-functioning, older populations. This paper describes the application of sleep fMRI as a way to study both extrinsic and intrinsic brain functions in autism between 12 and 36 months. Preliminary studies that use sleep fMRI method show that defects in the superior temporal gyrus (STG) in response to language are early emerging in autism and can be found in as young as 14 months in age. As such indices of abnormal early development of the STG may prove useful in the search for a biomarker of autism detectable during the infancy period. From a theoretical standpoint, examining sleep fMRI studies in autism gains some clarity when placed in context of the more established literature on structural brain development of autism which suggests that autism involves early brain overgrowth. Studies of plasticity in autism have yet to be done, but it is likely that the window of opportunity for altering the course of brain development in autism begins within the first year of life. The ability to do so relies on improving and streamlining early identification and thus early treatment efforts.

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1. Introduction

Functional magnetic resonance imaging (fMRI) is a powerful tool for studying two fundamental functional properties of the brain. First, it informs us about how the brain responds to environmental stimuli, or more simply, evoked function. As an evoked technique fMRI has confirmed long-held beliefs grounded in lesion studies: language processing is largely lateralized to the left side of the brain (Dehaene-Lambertz et al., 2006a) and face processing to the right (Haxby et al., 2000; Kanwisher et al., 1997); the amygdala is integral to processing fearful stimuli (Adolphs et al., 1995) and the hippocampus to memory retrieval (Wais, 2008) and so on. It has also brought new information such as the discovery that there are specific brain regions integral to the processing body parts (Peelen and Downing, 2005), places (Park and Chun, 2009) numerosity (Dormal et al., 2010), and even the experience of love (Beauregard et al., 2009). Second, fMRI is also capable of studying fundamental underlying neural organizational networks, or more simply, intrinsic function. It is now widely accepted that the brain is organized via multiple networks each with its own frequency during rest, a characteristic evident even while in a coma (Boly et al., 2008). This discovery can be traced back to an fMRI study conducted by Biswal et al. in (1995) and pioneered thereafter by Raichle et al. (2001). The so-called resting state functional connectivity approach has opened many opportunities for discovery because it taps into the previously unstudied intrinsic functioning of the brain that is thought to be independent of task or environment.

Autism is a developmental disorder impacting one out of every 100 children born today. It is a disorder that affects how the brain grows and works, yet the functional brain characteristics of autism during the time when symptoms first appear, namely 12-36 months, is almost completely unknown. This is because fMRI studies have been conducted almost exclusively with high functioning adolescents and adults with autism (for Review see (Minshew and Keller). The reason for this major gap in knowledge is that despite its power to map brain function, fMRI cannot be successfully used with awake, alert toddlers, whether autistic or typically developing. This is due to the strong requirement for subjects to remain still during an entire fMRI experiment, a task beyond that of infants and toddlers.

Recently, however, scientists have discovered a new way to understand brain function in infants and toddlers by examining the brain's functional signature using fMRI during natural sleep. When considering the study of autism, this method opens considerable doors because it eliminates biases of past studies that only sampled from high-functioning, older populations. This method, heretofore referred to as "sleep fMRI", was first used to map aspects of brain functioning in typically developing infants and toddlers in the early 2000s (Dehaene-Lambertz et al., 2002; Dehaene-Lambertz et al., 2006b). Although the brain's signal is attenuated during natural sleep in contrast to the awake state, the distribution is surprisingly similar (Dehaene-Lambertz et al., 2002; Wilke et al., 2003).

The sleep fMRI method enables both fundamental functional properties, evoked and intrinsic, to be examined in the very young developing autistic brain. As an evoked technique, examining language processing using sleep fMRI is ideal because defects in the emergence of language are among the earliest warning signs of autism. In contrast, most typically developing infants speak their first word by 12-months (Fenson et al., 1994) and can discriminate their native language from others within the first months of life (Moon et al., 1993), suggesting that the brain is eager to process language very early in development and its signature should be clearly evident. As an intrinsic technique it can be used to study resting networks in early development in autism because it is widely assumed that connectivity is abnormal in autism (Assaf et al., 2010; Cherkassky et al., 2006; Courchesne et al., 2007; Ebisch et al., 2010; Kleinhans et al., 2008b; Noonan et al., 2009).

Here I describe the application of sleep fMRI as a way to study both extrinsic and intrinsic brain function in autism between 12-36 months. I consider the merits of using sleep fMRI for biomarker discovery and discuss caveats as well. While the sleep fMRI literature is small, it gains some clarity when placed side by side with the more well-understood structural brain development of autism; in particular the idea that autism is characterized by brain overgrowth during the first year or two of life (Courchesne et al., 2003; Courchesne, 2004; Courchesne et al., 2007; Dementieva et al., 2005; Elder et al., 2008). This paper concludes by considering the idea that great strides can be made, including changing patterns of functional brain activity, if only autism could be identified and treated consistently prior to the emergence of full-blown symptoms.

2. The left temporal cortex: Poised and ready for language

Babies seem to be born ready to process language. Studies have found that newborns are able to discriminate sentences in different languages (Meler et al., 1988; Nazzi et al., 1998) and prefer to listen to their native language when given a choice (Moon et al., 1993).

Although various acoustic properties of speech are often processed bilaterally (Hickok and Poeppel, 2007) it has been hypothesized that it is the left side of the human brain that is anatomically poised to process and generate language