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Genetic influences on phase synchrony of brain oscillations supporting response inhibition

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ABSTRACT

Phase synchronization of neuronal oscillations is a fundamental mechanism underlying cognitive processing and behavior, including context-dependent response production and inhibition. Abnormalities in neural synchrony can lead to abnormal information processing and contribute to cognitive and behavioral deficits in neuropsychiatric disorders. However, little is known about genetic and environmental contributions to individual differences in cortical oscillatory dynamics underlying response inhibition. This study examined heritability of event-related phase synchronization of brain oscillations in 302 young female twins including 94 MZ and 57 DZ pairs performing a cued Go/No-Go version of the Continuous Performance Test (CPT). We used the Phase Locking Index (PLI) to assess inter-trial phase clustering (synchrony) in several frequency bands in two time intervals after stimulus onset (0–300 and 301–600 ms). Response inhibition (i.e., successful response suppression in No-Go trials) was characterized by a transient increase in phase synchronization of delta- and theta-band oscillations in the fronto-central midline region. Genetic analysis showed significant heritability of the phase locking measures related to response inhibition, with 30 to 49% of inter-individual variability being accounted for by genetic factors. This is the first study providing evidence for heritability of task-related neural synchrony. The present results suggest that PLI can serve as an indicator of genetically transmitted individual differences in neural substrates of response inhibition.

1. Introduction

Inter-individual variation in human cognition and behavior, both normal and abnormal, is strongly influenced by genetic factors (e.g., Beam and Turkheimer, 2013). However, neurobiological pathways and mechanisms mediating these genetic influences remain poorly understood. Investigating the genetic contribution to individual differences in neural mechanisms supporting specific cognitive function helps to establish meaningful links between genes, brain, and behavior. In particular, identification of heritable neurophenotypic markers for complex, higher order cognitive functions can facilitate finding genes for higher cognition characteristics by focusing analysis on well-characterized neurophysiological processes.

Neural mechanisms of cognitive control are important targets for genetic research because deficits in cognitive control and associated impairments in self-regulation of behavior have been observed in a broad range of psychopathologies including but not limited to schizophrenia, addictive disorders, and attention-deficit hyperactivity disorder (Barch, 2005). Genetic research on the etiology of these disorders has been hindered by the complexity and heterogeneity of diagnostic phenotypes. An alternative strategy is to focus on the identification of intermediate neural phenotypes, or "endophenotypes", that is, genetically transmitted variability of brain function mediating the association between the genotype and complex behavioral phenotype (Gottesman and Gould, 2003). A recent initiative of the National Institute of Mental Health focuses on the identification of "Research Domain Criteria (RDoC)", defined as novel brain-based dimensions that cut across diagnostic categories, better represent the underlying neurobiology (Insel et al., 2010), and are amenable to computational modeling (Stephan and Mathys, 2014). Response inhibition is one of such fundamental cross-diagnostic neurocognitive, with most notable deficits observed in the "externalizing spectrum" disorders characterized by impulsive and under-controlled behaviors such as oppositional-defiant and conduct disorders (children), antisocial personality disorder (adults), substance use disorders, and attention-deficit/ hyperactivity disorder (ADHD).

It has long been proposed that synchronization binds oscillatory neuronal assemblies into coherent functional networks that provide the basis for perception and action (Livanov, 1934, 1977). Empirical studies and computational modeling indicate that interactions between

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interconnected neurons comprising a functional network are state-dependent (e.g., Friston et al., 2012). In particular, the dynamic modulation of neuronal responsiveness determines the probability and timing of the generation of action potentials in functionally connected neurons (reviewed in Haider and McCormick, 2009). Animal models and research with human participants have demonstrated the central role of neural oscillations in the dynamic organization of functional networks. Precise temporal coordination of neuronal activity states is achieved through transient phase synchronization of oscillations in neuronal assemblies (Buzsaki and Draguhn, 2004; Klimesch et al., 2007; Livanov, 1977; Llinas et al., 2005; Sauseng and Klimesch, 2008; Uhlhaas and Singer, 2010, 2012). The development of methods for quantifying temporal neural dynamics has allowed researchers to demonstrate the functional significance of neuronal synchronization across a broad range of tasks, conditions, and cognitive processes including sensation, perception, attention, and memory (Benchenane et al., 2011; Klimesch et al., 2007; Livanov, 1977; Palva et al., 2010; Sauseng and Klimesch, 2008; Uhlhaas and Singer, 2010, 2012; Womelsdorf et al., 2007).

Recent studies underscore the role of neural synchrony in higher order, super-ordinate integrative functions such as cognitive control (Cohen, 2011; Nigbur et al., 2012; Nigbur et al., 2011). Nigbur et al. (2011) reported increased power of theta-band (4–8 Hz) oscillations related to conflict processing across different types of conflicts including response inhibition, perceptual conflict (stimulus incongruency), and response conflict. The largest effect was observed in the No-Go condition of the response inhibition task. Importantly, theta enhancement was localized in medio-frontal cortex (MFC) areas within anterior cingulate cortex and (pre-) supplementary motor areas (Nigbur et al., 2012; Nigbur et al., 2011). Other authors have proposed that theta oscillations generated in the medial prefrontal cortex represent a common neurophysiological substrate for the processing the signals of novelty, conflict, error, and punishment (Cavanagh et al., 2012), decision making, as well as action selection in goal-directed behavior (Womelsdorf et al., 2010b). Finally, individual differences in theta-band synchronization predict individual differences in cognitive functioning: lower inter-trial phase synchrony in the theta band predicted reduced stability of performance as indicated by reaction time variability (Papenberg et al., 2013), and long-range theta synchrony during cognitive tasks has been found to correlate with general intelligence (Anokhin et al., 1999).

These results are in good agreement with animal evidence. When rats had to choose between two action alternatives, cell assembly phase synchronization peaked at the decision point (Jones and Wilson, 2005). In a genetic mouse model of schizophrenia, hippocampal-prefrontal theta coherence in a spatial working memory task was drastically reduced, and lower theta coherence before training predicted the time it took the animals to learn the task (Benchenane et al., 2011; Sigurdsson et al., 2010). Synchronization of lower frequency (delta-band) oscillations also play an important role in higher cognitive processes such as decision making in monkeys (Nacher et al., 2013), and reduced event-related delta oscillations have been associated with mild cognitive impairment at the prodromal stage of Alzheimer's disease (Yener et al., 2013). Taken together, the available evidence indicates that low-frequency oscillations (delta and theta) play a key role in integrative brain activity supporting higher cognition, and that abnormal event-related oscillations are associated with cognitive deficits.

In a recent study, we demonstrated significant increase in phase synchronization in delta and theta bands in a Go/No-Go task, as well as both spatial and temporal dissociation between No-Go and Go conditions, such that No-Go stimuli produced stronger phase synchronization in the anterior scalp regions in a time window between 300 and 600 ms after stimulus-onset (Müller & Anokhin, 2012). Other studies also reported phase synchronization in No-Go trials at anterior sites (Beste et al., 2011; Papenberg et al., 2013). Response inhibition tasks produce two major ERP components that discriminate between the Go and No-Go trials. The first is the midline frontal N2. This component is restricted to No-Go trials, and has been observed consistently in visual and auditory tasks (Nieuwenhuis et al., 2004; Nieuwenhuis et al., 2003). The second is the frontal P300, a component that is substantially increased on No-Go trial; this phenomenon is labeled as "No-Go anteriorization" of P300 (Fallgatter and Strik, 1999; Roberts et al., 1994). The No-Go anteriorization has been proposed as a robust topographical marker of the activation of frontal circuitry related to response inhibition (Fallgatter et al., 1997). In experiments designed to separately manipulate conflict and inhibition, N2 and P3 components showed functionally dissociable effects, suggesting that N2 reflects a conflict between two competing response representations (e.g., execute or withhold a response), whereas P3 is increased only when planned movements need to be inhibited (Randall and Smith, 2011). Studies involving both fMRI and ERP measurement in the same Go/No-Go tasks have consistently associated the N2 component with the anterior cingulate cortex activation (Garavan et al., 2002; Mathalon et al., 2003; Swainson et al., 2003; van Veen and Carter, 2002a, b). In contrast, the anteriorized P3 observed in response inhibition condition has been linked to pre-supplementary motor areas presumably involved in motor-inhibitory mechanisms, rather than to conflict processing per se (Huster et al., 2011). The amplitudes of both N2 and P3 No-Go components are highly heritable, with 60 and 58% of inter-individual variability being attributable to genetic factors (Anokhin et al., 2004).

Our recent study suggests that the No-Go N2 component emerges as a result of phase locking of theta-band oscillations, whereas the P3 component is primarily reflecting synchronization in the delta band (Müller and Anokhin, 2012). There is substantial evidence for the functional significance of individual differences in the strength of neural synchrony including associations with cognitive and behavioral performance in both humans (Anokhin et al., 1999; Papenberg et al., 2013) and animals (Benchenane et al., 2011), as well as for the liability of neural synchrony to neuropsychiatric disorders such as schizophrenia, epilepsy, autism, Alzheimer's disease, and Parkinson's disease (reviewed in Uhlhaas and Singer, 2006, 2012). Converging evidence suggests that deficient temporal coordination of neuronal activity leads disrupts a variety of brain functions. In particular, abnormalities in stimulus-evoked neuronal synchronization have been described in schizophrenics and their first-degree relatives, suggesting that neural synchrony may serve as an endophenotype for schizophrenia (Uhlhaas and Singer, 2006, 2010). Neural synchrony is an important determinant of individual differences in normal brain function and behavior, as well as in pathophysiology of brain disorders.

However, surprisingly little is known about the genetic and environmental etiology of individual differences in phase synchrony during cognitive processing. Demonstrating heritability of task-relevant neural synchrony is a first step toward characterization of genetic factors influencing brain synchrony and, hence, core neurophysiological mechanisms of cognition. Here, we investigated heritability of neural synchrony related to response inhibition using a Go/No-Go task in a large sample of monozygotic and dizygotic twins. Neural synchrony was assessed using the phase locking index (PLI), a measure of inter-trial phase clustering of brain oscillations (Cohen and Gulbinaite, 2014).

2. Methods

2.1. Participants

The study sample consisted of 302 young adult female twins aged 18 to 28 years, including 94 MZ and 57 DZ pairs selected from the Missouri Family Registry. Zygosity was determined using a standard set of questions asked to both twins as is typically done in twin genetic research, lab technicians' rating of twins similarity, and, for about 70% of the sample, using genotyping data. Participants were excluded if they had a history of serious head trauma or were using psychoactive medication at the time of testing. All experiments on human research participants were conducted in accordance with the declaration of Helsinki. The