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Short Commentary Open Access

Impairment of Cognitive Function by Chemotherapy: Association with the Disruption of Phase-Locking and Synchronization in Anterior Cingulate Cortex

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Bipolar Disorder is a mentalbrain disorder, characterized by behavioral impulsiveness, shift in mood, energy and activity level. Patients with bipolar disorder demonstrate show cognitive deficits and disorganized behavior, which may reflect a disturbance in neural synchronization deactivation in rostral anterior cingulate cortex during euthymia [1] and are associated with comorbid anxiety and increased suicidal tendencies [2]. Anterior cingulate cortex (ACC) plays a pivotal role in cognitive learning, decision making and emotions. The structural and functional neuroimaging studies suggested that the ACC may be predominantly affected in these disorders [3]. Perigenual ACC has been reported to play a central role in bipolar disorder and to alter the default mode network (DMN) and salience network systems [4]. Bipolar disorder youth displayed greater theta oscillations in the ACC in response to frustration-inducing negative feedback [5]. During a verbal fluency task, tapping task and visual task another study showed that both the ACC and lateral PFC regions were often affected in bipolar patients [6]. A human resting-state whole brain functional connectivity investigation showed reduced complex ACC connectivity [7]. Further, previous electroencephalographic (EEG) studies have revealed reduced power across the frequencies of stimulation. Phase-locking across trials was also disturbed in bipolar disorder, consistent with poor phase synchronization between the stimulus and EEG [8]. However the pathophysiology of bipolar disorder is not yet fully understood.

In this commentary we discuss about the behavioral methods used in the paper "Impairment of Cognitive Function by Chemotherapy: Association with the Disruption of Phase-locking and Synchronization in Anterior Cingulate Cortex" by Li MU et al. [9] and its possible applications in understanding the neurophysiological changes in bipolar disorder.

The 'chemobrain' refers to a range of cognitive deficits caused by prolonged chemotherapy.

Li Mu and colleagues investigated chemotherapy associated with emotional and cognitive deficits [9]. The authors used a chronic rat model devoid of other illness by taking advantage of the single cytostatic agent cisplatin instead of a chemotherapeutic cocktail in a clinical setting and examined the cognitive functions for up to two months post treatment. This study shows that cisplatin-treated rats demonstrated produced anxiety- like behavior, and exhibited impaired spatial reference memory. Decision- making is a complex process involving different functions such as effort requirements, reward evaluation, reward occurrence and penalty associated with rewards. Hence, so the integration of several executive brain areas is a feature of good decision -making and has emerged as a crucial theme in neurophysiological studies of cognition. Poor decision- making is associated with other behavioral traits such as cognitive inflexibility, impulsive control disorder, emotional disturbance, risk taking and reward sensitivity. Therefore, so decision-making can be impaired in psychiatric disorders. Rat gambling task RGT showed decreases of the percentage of good decision-makers, and increases in the percentage of poor decision-makers, and delay-good decision-makers in cisplatin-treated rats. The study further examined the effect of cisplatin treatment on the modulation of brain synaptic transmission in animal model that may explain its influence on cognitive function.

Brain rhythms are likely to be a fundamental mechanism for modulating, filtering, and redirecting information in the nervous system. Neural oscillations play a basic role in coordinated activity during normal functional brain processes [10]. Induction of LTP is improved favorable when higher frequency electrical stimulations are targeting were arrived on the positive phase of theta oscillations, Behavioral studies in humans. Rutishauser et al. showed that successful memory formation in humans is predicted by a tight coordination of spike timing with the local theta oscillation. Rutishauser show that brain oscillations appears theta-frequency phase-locking with timing of single-neuron activity [11]. Moreover, moreover, synchronously discharging cells are more effective at driving neurons at subsequent processing stages [11,12]. Li Mu and colleagues [12] found that in control rats 44.2% of ACC neurons fired spikes that were phase-locked to the LFP oscillations in the theta range (8.03 Hz). In contrast, only 12.8% ACC neurons showed phase locking at theta range in the cisplatin group. It appears that the dysfunction of the phase-locking of the neural firing with the theta oscillation mediates the decision-making deficits following cancer chemotherapy in rats [12].

It has also become clear that event-related oscillations are modified in many types of neuropathology, in particular in cognitive impairment. This article provides the first direct evidence that cancer chemotherapy can reduce the coherence and interrupt the phase-locking of ACC neuronal spikes with the ongoing theta band of the local field potential. More importantly, the disruption of the synchronized theta oscillations and impairment of induction of long-term potentiation of the [WHAT???] in the basolateral amygdala (BLA)-ACC pathway are associated with emotional and cognitive deficits in the rats following cancer chemotherapy. It gives examples of applications of essential methods and concepts in bipolar disorder that provide a basis for fundamental notions regarding neurophysiologic biomarkers in cognitive impairment. We can take advantage of the electrophysiological techniques to understand the neurophysiology of behavior including risk- taking abilities, and decision- making in animal models of bipolar

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disorder, and also we can develop a stimulation therapy or medicine to reverse the neurophysiological changes due to induction of bipolar disorder.

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