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RESTING-STATE BRAIN NETWORKS REVEALED BY GRANGER CAUSAL CONNECTIVITY IN FROGS

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Abstract—Resting-state networks (RSNs) refer to the spontaneous brain activity generated under resting conditions, which maintain the dynamic connectivity of functional brain networks for automatic perception or higher order cognitive functions. Here, Granger causal connectivity analysis (GCCA) was used to explore brain RSNs in the music frog (*Babina daunchina*) during different behavioral activity phases. The results reveal that a causal network in the frog brain can be identified during the resting-state which reflects both brain lateralization and sexual dimorphism. Specifically (1) ascending causal connections from the left mesencephalon to both sides of the telencephalon are significantly higher than those from the right mesencephalon, while the right telencephalon gives rise to the strongest efferent projections among all brain regions; (2) causal connections from the left mesencephalon in females are significantly higher than those in males and (3) these connections are similar during both the high and low behavioral activity phases in this species although almost all electroencephalograph (EEG) spectral bands showed higher power in the high activity phase for all nodes. The functional features of this network match important characteristics of auditory perception in this species. Thus we propose that this causal network maintains auditory perception during the resting state for unexpected auditory inputs as resting-state networks do in other species. These results are also consistent with the idea that females are more sensitive to auditory stimuli than males during the reproductive season. In addition, these results imply that even when not behaviorally active, the frogs remain vigilant for detecting external stimuli. © 2016 IBRO. Published by Elsevier Ltd. All rights reserved.

Key words: resting-state network (RSN), Granger causal connectivity analysis (GCCA), vigilant, sexual dimorphism, frog.

INTRODUCTION

Advanced neuroimaging techniques have revealed several sets of brain areas that are synchronously active during the resting-state, which are known as resting-state networks (RSNs) (Damoiseaux et al., 2006; Niazy et al., 2015). These brain networks do not require a task to exhibit synchrony and in humans include those brain areas associated with the motor system (Biswal et al., 1995; De Luca et al., 2005; Xiong et al., 2009), visual processing (Greicius et al., 2003), and auditory perception (Hunter et al., 2006). The major function of RSNs is thought to be to maintain dynamic connectivity among related functional networks so that these may process internal and external signals automatically and reliably (Buckner and Vincent, 2007; Greicius and Menon, 2004; Raichle et al., 2001). Important higher order cognitive functions such as memory consolidation and self-referential processes also involve RSNs (Albert et al., 2009; Van Den Heuvel and Pol, 2010; Wicker et al., 2003), which allow individuals to review past experiences and plan future actions. RSNs similar or homologous to those of humans have been identified in monkeys (Belcher et al., 2013; Hutchison et al., 2012) and rodents (Lu et al., 2012; Sforazzini et al., 2014; Zhao et al., 2008). These findings suggest RSNs area primitive feature of the mammalian brain (Hutchison and Everling, 2012).

Although RSNs have been extensively studied in humans, monkeys and rodents, they have not been studied in any non-mammalian species. Many anuran neuroanatomical structures are believed to be homologous to structures in the mammalian brain although these are typically less differentiated (Butler and Hodos, 2005). Functional brain characteristics in mammals such as lateralization of function (Rogers, 2002; Vallortigara et al., 2011) have also been identified in anurans including visual asymmetry for foraging and predator avoidance (Lippolis et al., 2002; Vallortigara et al., 1998), right-limb preference (Rogers, 2000) and right-ear dominance for perception of conspecific calls (Fang et al., 2014; Xue et al., 2015). These functional similarities presumably exist because important neuroanatomical features have been conserved during vertebrate brain evolution (Allman, 2000; Finlay et al., 2001; Northcutt,

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Abbreviations: EEG, electroencephalograph; GCCA, Granger causal connectivity analysis; LM, left mesencephalon; LT, left telencephalon; non-REM sleep, non-rapid eye movement sleep; RM, right mesencephalon; RSN, resting-state network; RT, right telencephalon.

2002). Of interest here is whether the RSNs, the basic brain status during no-task periods (Raichle et al., 2001), also exist in anurans. Since all land vertebrates descended from an amphibian common ancestor, investigation of the brain networks of anurans during a non-task period may extend our knowledge of how functional networks in the vertebrate brain have evolved.

Previous electroencephalograph (EEG) studies in the Emei music frog (*Babina daunchina*) have revealed that frogs continually exhibit spontaneous brain activity in both the forebrain and midbrain throughout the entire light–dark cycle with the absence of external stimulation (Yang et al., 2014). These findings imply that brain activity in the midbrain and forebrain is intrinsic. Furthermore auditory stimuli induce activity in these brain areas (Fang et al., 2014), implying that spontaneous brain activities in these areas may be functionally related to form brain networks that involved in passive auditory perception.

Music frogs exhibit a “bigeminal” behavioral pattern which was categorized by a high activity phase (i.e. around dawn and dusk) and a low activity phase (i.e. around noon and midnight), synchronized with EEG patterns (Yang et al., 2014). These two phases are distinguished both by the degree of behavioral activity and EEG power. In the low activity phase the total number of behaviors performed is significantly lower than in the high activity phase, and in the low activity phase EEG power during a motionless period is significantly lower than during a motionless period in the high activity phase. In the low activity phase EEG spindle waves appear similar to those of non-rapid eye movement sleep (non-REM sleep) in higher vertebrates (Fang et al., 2012). In mammals brain networks are thought to function diffusely during sleep (Spoormaker et al., 2012; Tagliazucchi et al., 2013). Therefore we propose here that network connectivity in frogs will be weaker during the behaviorally low activity phase than during the high activity phase.

The present study investigated brain networks in terms of the magnitudes and directions of causal connections between the mesencephalon and telencephalon during the resting state in music frogs using Granger causal connectivity analysis (GCCA) based on EEG data. These GC values reflect information flows and can be used to build networks (Seth et al., 2015). We predict that (1) there are lateralized brain networks in the frog brain during the resting-state which are related to auditory perception consistent with previous studies documenting left hemisphere advantage in processing conspecific vocalizations (Fang et al., 2014; Xue et al., 2015); (2) these networks exhibit sexual dimorphism consistent with previous studies of circadian rhythms showing that the left hemisphere of females exhibits higher relative EEG power than that of males (Yang et al., 2014) and (3) these networks are stronger in the high activity phase than in the low activity phase.

EXPERIMENTAL PROCEDURES

Animal

Twelve music frogs (sex ratio = 1:1) were collected from several ponds in the Emei Mountain area (29.60°N,

103.36°E, elevation of 1315 m above sea level), Sichuan, China. The frogs were separated by sex and housed in two opaque plastic tanks (45 cm × 35 cm and 30 cm deep) containing about 3 cm water with mud placed around the walls about 5 cm high so that the frogs could shelter themselves. The tanks were placed in a room under controlled temperature ($23 \pm 1^\circ\text{C}$) and relative humidity (70–80%) with a 12:12 light–dark cycle (lights on at 08:00 h) using a fluorescent lamp. The animals were fed live crickets (bought from a pets’ fodder shop) every three days.

The experiments were conducted after the reproductive season ended. Reproductive status was induced for the subjects with intraperitoneal injections of gonadotropin-releasing hormone (GnRH-A6; Sichuan, China; 1.25 μg per animal) as described previously (Yang et al., 2014). After hormone injection, the frogs performed reproductive behaviors in response to playbacks of male advertisement calls; males competitively produced advertisement calls in response to playbacks and females approached the broadcasting speaker. Induction of reproductive status using this method typically persists for more than 3 days (Yang et al., 2014).

All experiments were in accordance with the Law of the People’s Republic of China on the Protection of Wildlife and approved by the Chengdu Institute of Biology Animal Care Committee.

Surgery

The detailed surgical procedures have been described in previous studies (Fang et al., 2012). In brief, four cortical EEG electrodes, composed of miniature stainless steels crews (ϕ 0.8 mm), were implanted on the frog skull: the left and right sides of the telencephalon and mesencephalon (R1, R2, R3, and R4; i.e. left telencephalon (LT), right telencephalon (RT), left mesencephalon (LM) and right mesencephalon (RM)), and referenced to the electrode above the cerebellum (P) (Fig. 1). After the operation, the subjects recovered for 5 days under the same housing conditions. At the end of the experiments, the subjects were euthanized by intraperitoneal injection of sodium pentobarbital, and hematoxylin dye was used to confirm recording electrode sites.

Data acquisition

An opaque plastic tank (80 × 60 cm and 55 cm deep) containing mud and water was used for the experiments and was placed in a soundproof and electromagnetically shielded chamber (background noise, 23.0 ± 1.7 dB). An infrared camera with a motion detector was mounted centrally about 1 m above the tank for monitoring the locomotor activity of the subject. Light intensity was set at 10.47×10^{-3} lux during the light phase and 0.04×10^{-3} lux during the dark phase. Electrophysiological signals were recorded with a signal acquisition system (Chengyi, RM6280C; Chengdu, Sichuan, China) for 24 h beginning at 20:00. The band-pass filter was set to 0.16–100 Hz for filtering EEG signals with a notch filter to eliminate possible interference at 50 Hz. A sampling rate of 1000 Hz was used.

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