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Published Version
doi:10.3389/fnana.2014.00013

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Neuronal activity (c-Fos) delineating interactions of the cerebral cortex and basal ganglia

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INTRODUCTION

The cerebral cortex and basal ganglia (BG), two of the largest forebrain structures, form a dynamic interactive network. The cerebral cortex, along with the thalamus and subcortical systems, sends signals to the BG. The BG in turn, with modulation from midbrain dopaminergic system, integrates and processes this cortical information for output, back to the cerebral cortex to shape cortical activity and ultimately affect cortical functions such as motor behavior (Yelnik, 2008). This reciprocal regulation is significantly altered after BG dysfunction, as in neurological disorders such as Parkinson’s disease. We found that neuronal activity (c-Fos) in the BG followed cortical activity, i.e., high in arousal state and low in sleep state. To determine if cortical activity is necessary for BG activity, we administered atropine to rats to induce a dissociative state resulting in slow-wave electroencephalography but hyperactive motor behaviors. Atropine blocked c-Fos expression in the cortex and BG, despite high c-Fos expression in the sub-cortical arousal neuronal groups and thalamus, indicating that cortical activity is required for BG activation. To identify which glutamate receptors in the BG that mediate cortical inputs, we injected ketamine [N-methyl-D-aspartate (NMDA) receptor antagonist] and 6-cyano-nitroquinoxaline-2, 3-dione (CNQX, a non-NMDA receptor antagonist). Systemic ketamine and CNQX administration revealed that NMDA receptors mediated subthalamic nucleus (STN) input to internal globus pallidus (GPI) and substantia nigra pars reticulata (SNr), while non-NMDA receptor mediated cortical input to the STN. Both types of glutamate receptors were involved in mediating cortical input to the striatum.

Dorsal striatal (caudoputamen, CPu) dopamine depletion by 6-hydroxydopamine resulted in reduced activity of the CPu, globus pallidus externa (GPe), and STN but increased activity of the GPi, SNr, and putative layer V neurons in the motor cortex. Our results reveal that the cortical activity is necessary for BG activity and clarifies the pathways and properties of the BG-cortical network and their putative role in the pathophysiology of BG disorders.

Keywords: cerebral cortex, basal ganglia, arousal, atropine, 6-hydroxydopamine, c-Fos, rat
Animals were anesthetized with chloral hydrate (350mg/kg) and a W condition. The sleep control group consisted of animals that did not have motor activity and that the cortex shapes BG activity via two pathways: NMDA and non-NMDA receptors. Our results suggest that cortical neuronal activity is necessary for BG neuronal activity and that the cortex shapes BG activity via two pathways: NMDA and non-NMDA receptor-mediated cortical inputs to the striatum, and non-NMDA receptor-mediated cortical inputs to the thalamus, GPe, and STN, but only during high cortical activity wakefulness. These changes in BG and cortical activity during dopamine depletion may underlie the various motor and non-motor symptoms of BG disorders, including Parkinson's disease.

**MATERIALS AND METHODS**

**ANIMALS**

Pathogen-free, adult, male Sprague–Dawley rats (275–300 g, Harlan) were individually housed and had ad libitum access to food and water. All animals were housed under light-controlled conditions (12 h light starting at 07:00 AM, 100 lux) in an isolated ventilated chamber maintained at 20–22°C, All protocols were approved by the Institutional Animal Care and Use Committee of Beth Israel Deaconess Medical Center and the experiments were carried out in accordance with the Guidelines laid down by the NIH in the US regarding the care and use of animals for experimental procedures. Every effort was made to minimize the number of animals used and any pain and discomfort experienced by the subjects.

**ACTIVE-WAKE (AW) CONDITION**

Four cages were aligned without covers in a hood, after saline or drug injection (see below), rats were allowed to freely move over and between cages. Under this social and motor-active condition, rats will remain awake and highly active for at least 4 h, as previously reported (Gompf et al., 2010). Rats were perfused 2 h after AW condition. The sleep control group consisted of animals that were perfused 2 h after saline injections around 9:00–10:00 AM. The perfused brains were processed for histology.

**6-HYDROXYDOPAMINE (6-OHDA) INJECTIONS**

Animals were anesthetized with chloral hydrate (500 mg/kg) and perfused with 50 ml saline followed by 500 ml 10% formalin through the heart. The brains were removed, post-fixed for 4 h in 10% formalin, and equilibrated in 20% sucrose in phosphate-buffered saline (PBS) overnight. The brains were frozen and sectioned on a freezing microtome at 40 μm into four series. Sections were washed in 0.1 M PBS, pH 7.4 (two changes) and then incubated in the primary antiserum (c-Fos, 1:50 K, AB5, Oncogene; choline acetyltransferase, ChAT, 1:500, AB144, Chemicon; tyrosine hydroxylase, TH, 1:20K, #22941, Diasonin) for 24 h at room temperature. On the second day, the sections were washed in PBS and incubated in biotinylated secondary antiserum (against appropriate species IgG, 1:1,000 in PBS) for 1 h, followed by a 1:1000 dilution of avidin-biotinperoxidase (Vector Laboratories, Burlingame, CA, USA) for 1 h at room temperature. The peroxidase reaction was visualized with 0.05% 3,3-diaminobenzidine tetrahydrochloride (DAB, Sigma) in PBS and 0.01% H2O2. The sections were stained brown with DAB or black by adding 0.05% cobalt chloride and 0.01% nickel ammonium sulfate to the DAB solutions. c-Fos was labeled black and TH and ChAT labeled brown to enable distinct staining within the same section. After terminating the reaction by PBS-azide, sections were mounted, dehydrated and cover slipped. As controls, adjacent sections were incubated without the primary antibody to confirm that no non-specific staining had occurred.

**CELL COUNTING**

c-Fos positive neurons were counted in the BG of three adjacent sections that contain BG structures. For the striatum, the 2.0 mm × 2.0 mm counting box was placed in the center of the dorsomedial striatum. For c-Fos counting in M1/M2 cortex, only black-stained large neurons (likely projecting pyramidal neurons) were counted in the entire M1/M2 cortex. For other BG subunits, we counted all c-Fos positive neurons in the entire region of three adjacent sections. The c-Fos counts represented by average counting per section per side were used to construct Tables 1 and 2. We used, paired T-test for count differences.
Table 1 | c-Fos expression in BG and cortex.

<table>
<thead>
<tr>
<th></th>
<th>Sleep</th>
<th>AW</th>
<th>Atropine</th>
<th>Ketamine</th>
<th>CNQX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum</td>
<td>15.6 ± 70</td>
<td>179.0 ± 15.2</td>
<td>23.5 ± 5.7**</td>
<td>75.7 ± 13.4**/##</td>
<td>134.3 ± 11.4**/##</td>
</tr>
<tr>
<td>GPe</td>
<td>5.8 ± 7.2</td>
<td>60.0 ± 7.9</td>
<td>8.4 ± 2.6*</td>
<td>25.0 ± 4.1**/##</td>
<td>8.7 ± 2.3**/##</td>
</tr>
<tr>
<td>GPi</td>
<td>2.2 ± 0.9</td>
<td>24.2 ± 5.5</td>
<td>2.0 ± 0.7**</td>
<td>4.2 ± 1.3**</td>
<td>3.43 ± 0.9**</td>
</tr>
<tr>
<td>STN</td>
<td>2.2 ± 1.6</td>
<td>97.8 ± 9.0</td>
<td>10.6 ± 3.2**/##</td>
<td>85.2 ± 8.2**##</td>
<td>6.2 ± 1.9**</td>
</tr>
<tr>
<td>SNr</td>
<td>1.8 ± 1.3</td>
<td>23.6 ± 4.3</td>
<td>1.8 ± 1.4**</td>
<td>1.9 ± 1.3**</td>
<td>2.2 ± 1.9**</td>
</tr>
<tr>
<td>LC</td>
<td>–</td>
<td>++++</td>
<td>Inactive</td>
<td>Active</td>
<td>Active</td>
</tr>
<tr>
<td>Cortex</td>
<td>Inactive</td>
<td>Active</td>
<td>Inactive</td>
<td>Active</td>
<td>Active</td>
</tr>
<tr>
<td>Thalamus</td>
<td>Inactive</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
<td>Active</td>
</tr>
</tbody>
</table>

LC: “+” = 25 c-Fos positive neurons. All c-Fos counting is presented by number/section/side. The difference *p < 0.05, **p < 0.01 of T-test is compared to the AW. The difference of #p < 0.05, ##p < 0.01 is compared to sleep condition.

Table 2 | c-Fos expression in intact (DA+/+) vs. DA depleted side (DA−/−) in AW *p < 0.05, **p < 0.01.

<table>
<thead>
<tr>
<th></th>
<th>DA+/+</th>
<th>DA−/−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Striatum</td>
<td>185.3 ± 16.2</td>
<td>95.4 ± 20.2*</td>
</tr>
<tr>
<td>GPe</td>
<td>55.2 ± 8.8</td>
<td>32.5 ± 13.1*</td>
</tr>
<tr>
<td>GPi</td>
<td>22.5 ± 6.8</td>
<td>75.9 ± 19.2**</td>
</tr>
<tr>
<td>STN</td>
<td>105.8 ± 12.6</td>
<td>64.7 ± 8.5*</td>
</tr>
<tr>
<td>SNr</td>
<td>26.1 ± 5.5</td>
<td>75.3 ± 12.2**</td>
</tr>
<tr>
<td>M1–M2</td>
<td>15.0 ± 10.1</td>
<td>38.7 ± 15.8**</td>
</tr>
</tbody>
</table>

RESULTS
CORTICAL ACTIVITY PREDICTS BG ACTIVITY

Although we have previously shown c-Fos expression in the BG during spontaneous and methamphetamine-induced wake (Vetrivelan et al., 2010), we sought to determine c-Fos expression in the BG during an active-wake (AW) condition, in which rats remain spontaneous active awake in the sleep period (8:00 AM–12:00 PM) and engage in social and motor behavior (see Materials and Methods). To determine BG activity in the AW condition, we injected saline and perfused rats in two conditions: after 2 h of sleep (N = 5) or after 2 h of AW (N = 5), during which animals had high locomotion and social interactions. Animals were perfused between 11:00 AM and 12:00 PM. The perfused brains were sectioned at 40 μm in four series, and two series of sections each were double immunolabeled with c-Fos (black color) and TH (brown color), or c-Fos (black color) and ChAT (brown color), respectively.

Compared to the sleep condition, c-Fos expression was significantly higher in the cerebral cortex in AW rats, especially in the prefrontal and frontal, motor, and sensory cortices (Table 1; Figure 1A) and in all the subunits of the BG, i.e., the dorsal striatum (i.e., caudoputamen, CPu), GPe, GPi, STN, and SNr (Table 1; Figures 1B–F). There was a distinct pattern of c-Fos expression in the dorsomedial part in the striatum that receives inputs from the premotor (M2) and primary motor (M1) cortices (Figure 1B). The medial part of the GPe, GPi, SNr, and STN also showed strong c-Fos expression (Table 1; Figures 1C–F). The pattern and amount of waking c-Fos expression were similar to that following methamphetamine injection but much higher.
than spontaneous wakefulness (Vetrivelan et al., 2010). These results indicate that BG neural activity is increased when cortical neuronal activity is increased and likewise decreased when cortical activity is decreased, as in the slow-wave EEG state like sleep.

CORTICAL ACTIVITY IS NECESSARY FOR BG ACTIVITY

To determine whether cortical activity is necessary for BG activity, we injected atropine, which induces a unique dissociative behavioral state with slow-wave EEG but heightened locomotion (Irmis, 1971; Davis et al., 2011). This “sleepwalking-like” state provides a unique opportunity to investigate whether cortical activity is necessary for BG activity. We injected atropine (100 mg/kg) at 9:00–10:00 AM and perfused the rats 2 h post-injection. The brains were sectioned, and the sections were immunolabeled with c-Fos and ChAT. Slow-wave EEG shown by atropine administration (Schaul et al., 1978) was confirmed by our EEG/EMG/video recording from two rats (Figure 2). Inconsistent with slow EEG, c-Fos expression in the cortex was very low (Figure 3A) and comparable to low c-Fos expression in the cortex in sleep condition (Table 1). In contrast, c-Fos was highly expressed in sub-cortical arousal regions such as the thalamus (intralaminar and midline region, Figure 6A), basal forebrain cholinergic neurons (Figure 6C), the tuberomammillary nucleus (TMN; Figure 6E), and the locus coeruleus (LC; Figure 6G), all resembling the pattern of c-Fos present in these areas during AW (Table 1). Along with low cortical activity, and despite high sub-cortical arousal activity, c-Fos expression in all BG sub-units, following low cortical c-Fos expression, was low (Table 1; Figures 3B–F), resembling the sleep condition. These results
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FIGURE 4 | Ketamine (NMDA receptor antagonist) suppresses corticostriatal inputs. c-Fos expression in cortex (A), CPu (B), GPe (C), GPi (D), STN (E), and SNr (F) after subanesthetic ketamine administration. Despite c-Fos positive neurons are abundant in cortex (A), c-Fos activity in the striatum (B), and GPe (C) is significantly reduced, compared to AW, but is higher than sleep condition, on the other hand, c-Fos activity in the STN (E) is comparable to the AW condition. Fos expression in the GPi (D) and SNr (F) is similar to sleep condition (see Figure 1; Table 1). These results suggest that the NMDA receptors are mostly responsible for cortical control of the striatum and GPe, and entirely responsible for STN control of GPi/SNr.

indicate that despite active subcortical arousal (locomotion) and active subcortical inputs to the BG, which was inactive when cortex was silenced. Thus cortical activity is necessary for BG neuronal activity.

NMDA RECEPTORS MEDIATE CORTICAL INPUTS TO THE CPu

We hypothesized that the cortex activates BG subunits by activating the striatum and the STN first via direct projections. Cortical input to the BG employs NMDA receptors as part of glutamatergic pathways (Ravenscroft and Brotchie, 2000). As these pathways potentially mediate cortical control over the BG, we examined whether NMDA and non-NMDA receptors are involved in both cortico-striatal and cortico-STN pathways, as well as pathways within the BG.

We administrated ketamine, a NMDA receptor antagonist, at a sub-anesthetic dose (35 mg/kg) to five rats in 9:00–10:00AM. As described before (Lu et al., 2008), animals were awake and active but rarely jumped to the other cages. Animals were perfused 2 h post-injection and the brains were sectioned and immunolabeled with c-Fos and TH. Ketamine at this dose increased locomotor behavior, wake-like EEG, and high c-Fos expression in arousal system structures including orexinergic neurons of the hypothalamus, LC, TMN, cortex, and thalamus, as previously demonstrated (Lu and Greco, 2006; Lu et al., 2008). Despite the increased c-Fos in the cortex, subcortical arousal systems, and thalamus system (Table 1; Figure 4A), as well as the presence of arousal behavior, c-Fos expression was lower in the CPu, GPi GPe, and SNr than during AW, although c-Fos in the CPu and GPe was higher than during sleep or atropine condition (Figures 4B,F; Table 1). The STN showed high c-Fos expression, similar to the AW condition (Table 1; Figures 4C–E). These results suggest that NMDA receptors are involved in mediating cortical glutamate inputs to the CPu and STN glutamate inputs to the GPe, GPi, and SNr but not cortical glutamate inputs to the STN (Figure 9A). However, the finding that c-Fos in the CPu and GPe was higher than in atropine and sleep condition suggests

FIGURE 5 | CNQX (non-NMDA receptor antagonist) suppresses corticosubthalamic inputs. After CNQX administration, c-Fos is highly expressed in cortex (A) and striatum (B) while c-Fos in the GPe (C), GPi (D), STN (E), and SNr (F) is very low, similar to sleep condition (see Figure 1; Table 1). Because of Fos expression in the striatum (B) is higher than ketamine condition and less than AW, we hypothesize that both NMDA and non-NMDA receptors are involved in mediating cortical input to the striatum, with dominant control from the NMDA receptors. Low Fos activity in the STN indicates that non-NMDA receptors mediate cortical input to the STN. Low Fos in the STN may result in low Fos activity in the GPe, GPi, and SNr.
non-NMDA receptors may also be involved in inputs to these structures.

**NON-NMDA RECEPTORS MEDIATE CORTICAL INPUTS TO THE STN**

As NMDA receptors do not appear to entirely mediate cortical input to the striatum and STN input to the GPe, we examined the role of non-NMDA AMPA/kainate receptors in mediating glutamatergic cortical inputs to the BG. We injected CNQX, an AMPA/kainate receptor antagonist (3.0 mg/kg) at 9:00–10:00 AM in five rats and perfused those 2 h post-injection. The brains were sectioned and immunolabeled with c-Fos.

Until perfusion time, rats with CNQX injections were awake but appeared to have difficulty with locomotion; their body posture suggested low muscle tone (partial paralysis). c-Fos expression in the cortex and thalamus, as well as subcortical arousal systems including the TMN, LC, and BF were comparable to the ketamine and AW condition (Table 1; Figures 5A and 6B,D,E,H).

**DOPAMINE DEPLETION ALTERS BG AND CORTICAL ACTIVITY DURING ACTIVE WAKE**

The CPu receives dopaminergic input from the substantia nigra pars compacta (SNc). To determine how this input regulates the BG, we selectively destroyed SNc dopamine efferents to the BG by unilaterally injecting 6-OHDA into the ventral GPe in five rats. This lesion method has also been used and been verified recently in behavioral tests (Abedi et al., 2013). After the rats recovered from surgery, we examined the role of dopamine depletion on cortical input to the BG using two conditions: high cortical activity (2 h of AW starting at 9:00–10:00 AM) and low cortical activity (2 h...
FIGURE 8 | Dopamine depletion evenly reduces c-Fos expression in the striatum. After unilateral striatal dopamine depletion, c-Fos expression in the striatum in AW is reduced in the lesion side, compared to the intact side.

(A) c-Fos counts (B) and normalized value (count–average)/average (C) in four striatal counting areas indicate the reduction of c-Fos positive neurons by 6-OHDA is evenly distributed across the striatum.

of sleep starting at 9:00-10:00 AM). After AW or sleep conditions, animals were perfused, and two series of sections were separately labeled with TH and c-Fos.

Tyrosine hydroxylase immunoreactivity showed selective loss of TH terminals in the dorsal striatum (caudate and putamen) of the 6-OHDA-injected animals, indicating dopamine depletion. The ventral striatum (nucleus accumbens and olfactory tubercle) and the dopaminergic neurons and terminals in the hypothalamus and amygdala were intact. In addition, LC TH-labeled neurons were intact.

In the high cortical activity AW condition, the number of large and intensely c-Fos-stained neurons in motor cortex M1 and M2 putative layer V neurons were higher in the lesioned side than the unlesioned side (Table 2; Figure 7A). Compared to the unlesioned side, dopamine depletion greatly reduced overall the number of c-Fos stained neurons in the CPu (Table 2; Figure 7B). c-Fos reduction appeared to be even across the striatum (Figure 8). Likewise, the number of c-Fos stained neurons in the GPe and STN was substantially reduced (Figures 7C,E). In contrast, the number of c-Fos positive neurons in the GPi and SNr of the lesioned side was twice that of the unlesioned side (Table 2; Figures 7D,F).

In the low cortical activity sleep condition, we again observed loss of TH terminals in the dorsal striatum, with preserved TH expression in the ventral striatum, hypothalamus, amygdala, and LC. In contrast to the AW condition, in the low cortical activity sleep condition c-Fos expression in the BG in both lesioned and unlesioned sides was uniformly low, without any differences between the sides (data not shown). These results indicate that dopamine depletion alters BG activity during high cortical activity, but not during low cortical activity.

DISCUSSION

We have demonstrated that BG (CPu, GPe, GPi, SNr, and STN) neuronal activity was synchronized to, and driven by, cortical neuronal activity via two routes, corticostriatal and corticostriatal projections; the STN then activated the GPe, SNr, and GPi to complete the cortex-BG synchronization (Figure 9A). NMDA and non-NMDA receptors mediated cortical glutamatergic inputs to the striatum as well as STN inputs to the GPe; NMDA receptors mediated STN inputs to the SNr and GPi; non-NMDA receptors mediated cortical inputs to the STN (Figure 9A). Dopamine depletion reduced activity in the CPu, GPe, and STN but increased activity in the GPi, SNr, and motor cortex (Figure 9B). These changes were particularly prominent in the active arousal conditions.

We used c-Fos as a marker of neuronal activity, although there are some limitations with using c-Fos. For example certain
neurons such as pontine cholinergic neurons, midbrain dopaminergic neurons and pontine serotonergic neurons do not show robust c-Fos staining (Lu et al., 2006). On the other hand, studies in sleep-wake system, circadian and feeding regulation indicate that c-Fos in other brain regions correlate with neuronal firing activity. Notably, all brain areas in our study are able to express c-Fos, which suggests that c-Fos in these areas reflects neuronal activity. And, importantly, we examined the contrast in c-Fos expression in the same area between conditions.

BG subunits are more active (firing rates) during cortically active states like wake and REM sleep (Magill et al., 2000; Urbain et al., 2000; Lee et al., 2001). Even during sleep, striatal, GPe and STN firing activity all follow up and down states of slow oscillatory cortical activity (Magill et al., 2000; Urbain et al., 2000; Lee et al., 2001; Kasanetz et al., 2002; Mahon et al., 2006). The responses of BG (CPu, GPe, GPI, STN, and SNr) neurons to a single cortical stimulation exhibit a sequential activity pattern of excitation-inhibition-excitation (Kita and Kita, 2011). The first excitation of BG neurons results from direct cortical projections to the striatum and STN, which then stimulates GPI, GPe, and SNr (Tachibana et al., 2008). The subsequent inhibition and excitation are likely mediated by intra-BG interactions (Asharpour, 1985; Rouzaire-Dubois and Scarnati, 1985). While BG and cortex appear synchronized, it was unclear whether activity of BG subunits depended on active cortical input or if subcortical input was sufficient to drive BG activity. Systemic atropine administration produced a dissociative state of cortical inhibition, subcortical activation, and BG inhibition, suggesting that the cortical inputs, rather than subcortical inputs, are required and necessary to drive overall BG activity. Subcortical inputs to the BG, including midbrain dopaminergic, pontine serotonergic and thalamic glutamatergic projections, may modulate BG activity during cortically active states. These results suggest that the BG activity is driven by cortical activity. Moreover, without active cortical inputs to the BG, such as during sleep or anesthesia, dopamine has a minimal role in modulating BG activity.

Aberrant or diminished cortical activity, such as those observed in the motor cortex in MPTP-treated primates, is thought to produce Parkinsonian symptoms (Goldberg et al., 2002; Johnson et al., 2009; Pasqueraye and Turner, 2011). However, 6-OHDA lesions of SNc in rats increase firing rates of the prefrontal pyramidal neurons in vitro (Zhang et al., 2011) and in vivo (Fan et al., 2011), which is consistent with our observation of high Fos expression in the motor cortex after 6-OHDA lesion. We also observed diminished striatal, GPe, and STN activity, along with hyperactivity in the GPI and SNr with dopamine depletion during active wake. The GPI/SNr hyperactivity may be due to loss of D1 action in the striatonigral neurons and/or hypoactive GPe, while hypoactivity in the STN may be caused by loss of direct dopamine D5 receptor action in the STN neurons (Ni et al., 2001; Baufreton et al., 2003). The BG can access cortex (Figure 9B) via the GPe directly (Parent and De Bellefeuille, 1983; Saper, 1984; Haber et al., 1985; Hur and Zaborszky, 2005; Vetrivelan et al., 2010), or indirectly through the mediodorsal thalamic nucleus (MD) (Haber et al., 1985). In addition, the motor thalamus relays SNr/GPI signals to the cortex. Hyperactivity of the GPI/SNr may influence motor cortex via this pathway, resulting in dyskinesia, postural instability, and difficulty turning the body in Parkinsonism. We could not detect c-Fos expression changes in the motor thalamus in the dopamine depletion condition, suggesting that GPI/SNr hyperactivity produces a subtle alteration of firing patterns rather than complete silencing of activity to influence thalamocortical projections.

In summary, our data supports the notion that cortical activity but not subcortical activity is required for BG activation. Specific
glutamate receptors are involved in cortical control of the BG, as well as the interaction of BG subunits and ultimately BG output back to cortex. By regulating BG activity during active states, dopamine influences cortical activity to affect sleep-wake and motor behavior.

ACKNOWLEDGMENTS

This study was supported by the NIH (NS06184, NS062727), National Natural Science Foundation of China (31171049, 31210161, 31271164), Shanghai Committee of Science and Technology (112Z1101800, 13410903100, 13dz2260700), SRF for ROCS, SEM, National Basic Research Program of China (2011CB711000, 2009ZX09303-006), and by Shanghai Leading Academic Discipline Project (B119).

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 21 January 2014; accepted: 03 March 2014; published online: 26 March 2014.


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