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Recruitment of Prefrontal-Striatal Circuit in Response to Skilled Motor Challenge

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Abstract

A variety of physical fitness regimens have been shown to improve cognition, including executive function, yet our understanding of which parameters of motor training are important in optimizing outcomes remains limited. We used functional brain mapping to compare the ability of two motor challenges to acutely recruit the prefrontal-striatal circuit. The two motor tasks—walking in a complex running wheel with irregularly spaced rungs or walking in a running wheel with a smooth internal surface—differed only in the extent of skill required for their execution. Cerebral perfusion was mapped in rats by intravenous injection of [14C]-iodoantipyrine during walking in either a motorized complex wheel or in a simple wheel. Regional cerebral blood flow (rCBF) was quantified by whole-brain autoradiography and analyzed in 3-D reconstructed brains by statistical parametric mapping and seed-based functional connectivity. Skilled or simple walking compared to rest, increased rCBF in regions of the motor circuit, somatosensory and visual cortex, as well as the hippocampus. Significantly greater rCBF increases were noted during skilled walking than for simple walking. Skilled walking, unlike simple walking or the resting condition, was associated with a significant positive functional connectivity in the prefrontal-striatal circuit (prelimbic cortex–dorsomedial striatum) and greater negative functional connectivity in the prefrontal-hippocampal circuit. Our findings suggest that the level of skill of a motor training task determines the extent of functional recruitment of the prefrontal-cortico-striatal circuit, with implications for a new approach in neurorehabilitation that uses circuit-specific neuroplasticity to improve motor and cognitive function.

Keywords

rehabilitation; exercise; motor skill learning; motor adaptation; functional brain mapping; functional connectivity; prefrontal cortex; striatum

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INTRODUCTION

A variety of physical fitness regimens have been shown to improve cognition in aging individuals, as well as to delay the onset of dementia in the cognitively impaired [1–4]. One way exercise types differ is in the extent of motor skill and aerobic challenge required for their execution, yet few studies have compared cognitive benefits between different exercise modalities or examined ‘skill’ as a parameter of motor training. While exercise is widely accepted to promote neuroplasticity in the brain, animal work suggests that different types of exercise affect the brain differently [5,6]. Specifically, aerobic exercise increases the density of blood capillaries (angiogenesis) and birth of new neurons (neurogenesis). Conversely, skilled exercise increases neuronal sprouting and synaptogenesis, important for re-establishing brain circuits impaired in disease states and required for normal behaviors, including cognition. Recent clinical studies suggest that executive functions (a critical component of mental flexibility, reasoning and problem solving, as well as for the shaping of motor functions) benefit from coordination training or simultaneous cognitive-physical training compared to exclusively cardiovascular training [7–9].

Prefrontal cortex (PFC) is well known to play a central role in cognition, and especially in executive function. Its importance in guiding motor learning—both during healthy aging, as well as during the neurorehabilitation of brain disorders—is less well understood. Our aim was to use functional brain mapping to compare the ability of two different motor tasks to engage the prefrontal-striatal circuit. The two tasks—walking in a complex, motorized running wheel with irregularly spaced rungs or walking in a motorized running wheel with a smooth internal surface—differed only in the extent of skill required for their execution. Walking in the complex wheel is highly demanding, requiring constant attention and rapid adjustment of footsteps. In contrast, walking in the smooth wheels is a simpler task requiring only a modest aerobic effort and less cognitive engagement. We hypothesized that skilled motor challenge compared to the simple motor challenge would acutely elicit greater functional recruitment of the PFC and increase functional connectivity in the prefrontal-striatal circuit.

METHODS

Skilled and aerobic motor training

Experimental procedures were approved by the University of Southern California’s Institutional Animal Care and Use Committee, which is accredited by the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC), International. All possible steps were taken to avoid the animals’ suffering at each stage of the experiment. Adult, male Sprague Dawley rats 10 weeks of age were obtained from the vendor (Harlan Laboratories, Indianapolis, IN, USA) and housed in pairs on a 12-hr light/12-hr dark cycle with free access to water and rodent chow. Animals were habituated to walking in a motorized wheel (36.5 cm diameter, model 80806, Lafayette Instruments, Lafayette, IN, USA). On the first day of habituation, walking was initiated at 1 m/min (3 trials of 5 min. each, intertrial rest period of 1 min.). The following day exposure continued at 1, 2, and 3 m/min, each for 5 min. trials.

Vascular cannulation

Following completion of the habituation, rats were anesthetized under isoflurane (2.5%) and using sterile procedure, the external jugular vein was cannulated with a silastic catheter (3.5 French), with the port at its distal end externalized dorsally in the region rostral to the scapula. Functional brain mapping was initiated 4 days post-operatively.

Functional brain mapping—Animals were randomized to one of two groups that were imaged while walking, either in wheels with an inner smooth plastic ‘floor’ covering the rungs (n=6) or in a complex wheel with irregularly spaced rungs, which demanded the constant adaptation of stride length (n=6). These motor challenges differ by the level of motor complexity, rather than by differences in physical expenditure. Our group has introduced the complex wheel as a means of delivering skilled motor training that is standardized and more quantifiable than exposure to an enriched environment [10]. In these wheels, a pseudo random pattern of rung spacing is achieved by repeating a pattern OOOXOX (O indicates a rung, X indicates a missing rung) (Fig. 1). An additional control group consisted of rats that were habituated to the wheel, as noted above but that were imaged at rest.

Radiotracer infusion—Time of day and duration of testing, persons performing the testing, lighting, ambient sound levels, room temperature were kept constant between sessions. Olfactory cues were minimized by wiping the treadmill with a 1% ammonia solution. Animals were transferred to the experimental room for 60 minutes in their home cage. Rats were then connected via the venous catheter to a lightly tethered cannula extension and motorized infusion pump, and then placed into an immobilized walking wheel for 5 minutes. Thereafter, walking was initiated at 4 m/min in the respective motorized wheel (complex or simple). After two minutes of walking, rats received an I.V. bolus of [^{14}C]-iodoantipyrine (300 μl @ 2.25 ml/min, 100 $\mu\text{Ci/kg}$, American Radiolabelled Chemicals, Saint Louis, MO, USA), followed immediately by the euthanasia agent (0.7 ml, pentobarbital 50 mg/mL, 3 M potassium chloride, I.V.). This resulted in cardiac arrest within ~ 10 s, a precipitous fall of arterial blood pressure, termination of brain perfusion, and death [11]. This approach uniquely allowed a 3-D assessment of functional activation in the awake, unrestrained rat, with a temporal resolution of ~ 10 s and an in-plane spatial resolution of 100 μm^2 . Comparison was made to rats that were imaged while resting in an immobilized wheel (n=6).

Autoradiography—Brains were flash frozen and serially sectioned (20- μm coronal slices, 300- μm interslice distance). Sections were exposed to Kodak Biomax film along with 16 radioactive ^{14}C standards (GE Healthcare, Chicago, IL, USA). Autoradiograms of brain slices were digitized and CBF-related tissue radioactivity was measured by the classic [^{14}C]-iodoantipyrine method [12]. In this method, there is a strict linear proportionality between tissue radioactivity and CBF when data is captured within a brief interval (~10 sec.) after the tracer injection [13].

Image processing—Each 3-D brain was reconstructed from 58 digitized autoradiograms (voxel size: 40×300×40 μm^3) using TurboReg [14] and a nonwarping geometric model that

includes rotations, translations and nearest-neighbor interpolation. A brain template was created using our prior methods [15], in which the background and ventricular spaces were thresholded based on their optical density. Spatial normalization consists of a 12-parameter affine transformation followed by nonlinear spatial normalization using 3-D discrete cosine transforms. Normalized brains were smoothed by a Gaussian kernel (FWHM=3× voxel size). To account for global differences in absolute amount of radiotracer, voxel intensities of each brain were scaled to a single mean.

Whole brain analysis of regional brain activation [15]—Data was analyzed in 3-dimensionally (3-D) reconstructed brains by statistical parametric mapping (SPM 5) [16] and seed-based functional connectivity using our prior methods [10,17]. Significance changes in regional cerebral blood flow (rCBF) were determined at $p < 0.05$ at the voxel level with an extent threshold of 100 contiguous voxels, which reflects a balanced approach to control Type I and Type II errors. Regions were identified using a rat brain atlas [18]. The directionality of rCBF changes was analyzed with nonbiased, voxel-by-voxel Student's *t*-tests.

Seed correlation analysis—We used SPM to evaluate significant correlation in rCBF ($p < 0.05$, extent threshold > 100 contiguous voxels) for the PFC across the whole brain in each group of animals. A region of interest (ROI) for the right prelimbic cortex was drawn manually in MRIcro (Rorden, Open source software, <http://www.cabiatl.com/mricro/mricro/>) over the template brain according to the rat brain atlas [18]. A functional ROI was created by combining the anatomical ROI with the corresponding significant SPM cluster by logical conjunction. Mean optical density of the ROI was extracted from each brain using the Marsbar toolbox [19]. Significant correlations were interpreted as functional connection and displayed as color-coded statistical parametric maps superimposed on the brain coronal slices.

RESULTS

SPM analysis (Fig. 2) showed that animals engaged in either the skilled or simple walking task compared to animals at rest, increased rCBF in regions of the motor circuit, including primary motor cortex (M1), dorsolateral striatum, thalamus (ventrolateral, lateral dorsal nuclei), red nucleus, zona incerta, and the cerebellar vermis. Increased rCBF in both the skilled or simple walking task was noted also in sensory regions, including primary somatosensory cortex of the forelimb (S1FL), hindlimb (S1HL), trunk (S1Tr), as well as in primary and secondary visual cortex (V1, V2). Rats walking in both the complex or simple wheels compared to animals at rest also demonstrated increases in rCBF of the posterior hippocampus (CA1, dentate gyrus) and septohippocampal nucleus. Although the percentage change in rCBF was modest (range 2–7%), the results were significant, with clusters of 100 or greater contiguous voxels significant at $p < 0.05$ to 0.0005. Additional measures contributing toward the confidence of effects detected included the presence of left–right symmetry and the correspondence of clusters of significant regions of interest within the boundaries of known anatomical structures. Significantly greater rCBF increases were noted in the aforementioned motor regions (except in the red nucleus) during walking in the complex wheel than for walking in the simple wheel (range 2–5%, Fig. 2). Rats walking in

the complex wheel compared to animals at rest demonstrated decreases in rCBF in midline frontal cortex (prelimbic, cingulate, retrosplenial cortices), sensory cortex (secondary somatosensory, auditory), and the amygdala (basolateral, basomedial, lateral). Similarly, simple walking compared to resting controls resulted in decreased rCBF in sensory cortex (secondary somatosensory, auditory) and the amygdala (basolateral, basomedial, lateral). However, here decreases in prelimbic and cingulate cortices were less marked, and even were increased in posterior retrosplenial regions of midline cortex.

Additionally, simple walking compared to resting controls resulted in decreased rCBF in the ventroposterolateral thalamic nucleus, the right subthalamic nucleus, the cortical amygdala, lateral cerebellum, as well as increased rCBF in the septum.

Correlation analysis using a prelimbic cortical seed showed greater positive functional connectivity of prelimbic cortex with the anterior, dorsomedial striatum, and greater negative functional connectivity of prelimbic cortex with the posterior hippocampus in animals walking in the complex wheel compared to those walking in the simple wheel or to animals at rest (Fig. 3). Significant anticorrelation of the PFC and hippocampus was confirmed with a seed placed in the ventral, posterior hippocampus (data not shown).

DISCUSSION

Our study compared functional brain activation during skilled and simple walking. Unique about our paradigm was the ability to apply whole brain imaging in awake, unrestrained animals during a task that required quadrupedal motion. Walking compared to the resting condition increased rCBF in regions within the basal ganglia thalamocortical motor circuit and in somatosensory regions, as previously reported [10,15]. These activations were greater during walking in the complex wheel than in the simple wheel, suggesting greater functional activation of these regions.

A motor challenge that required skill resulted in a differential functional recruitment of the prefrontal-striatal circuit compared to a motor challenge with lower skill requirements. The skilled motor task compared to the simple task elicited greater rCBF within the motor circuit (primary motor cortex, dorsolateral-striatum, ventrolateral thalamus, cerebellum) and primary somatosensory cortex (S1), while significantly greater decreases in rCBF were noted in midline cortex (prelimbic cortex, cingulate cortex). Seed analysis revealed a significant positive functional correlation between the prelimbic cortex and dorsomedial striatum during the skilled task, which was greater than that noted during the simple task. The observed increase in functional connectivity of the prelimbic-striatal circuit during skilled walking was consistent with the known topographic organization of corticostriatal inputs, in which prelimbic cortex provides direct inputs to the dorsomedial, ventromedial striatum [20].

Interestingly, functional connectivity increased in the PFC-striatal circuit, whereas regional CBF decreased in the PFC. More commonly, increases in functional connectivity are accompanied by increases in rCBF. It is noteworthy, however, that changes in synchrony do not have to be directly coupled to local changes in flow or metabolism. An overall reduction

in connectivity to other circuits can occur in concert with an increase in connectivity within a highly localized circuit, and thus, result in a net decrease in regional metabolic demand. Our results are in line with recent work by Eggenberger et al. who showed that 8 weeks of skilled motor training (dancing) compared to balance and stretching training elicits a greater reduction in PFC activation when subjects were imaged during a walking task using near infrared spectroscopy [8]. Our findings support the notion that the basal ganglia are significantly influenced by inputs from the PFC, which in the cognitive literature on executive function have been proposed to provide a top-down control signal for guiding the resolution of response competition that amplifies one response command and suppresses competing commands. Electrophysiologic and metabolic studies would be needed in the future to determine if the decrease in rCBF in the prelimbic cortex, alongside the increase in functional connectivity of the prelimbic–striatal circuit is the result of such differential neuronal suppression and amplification and/or if modifications in the rate of aerobic glycolysis or glucose utilization under different training regimens could account for these signal changes [21,22].

Prelimbic cortex and its striatal efferents on dorsomedial striatum are a key circuit in the rodent brain for goal-directed learning [23,24]. Our results in agreement with our earlier work in a rat model of Parkinsonism (bilateral partial dopaminergic deafferentation of the dorsal striatum). In the lesioned animals, 4 weeks of daily motor training resulted in greater functional connectivity of the PFC to the striatum and motor cortex when rats were trained in a complex versus a simple wheel [10]. This increase in functional connectivity was observed when animals were imaged during horizontal walking, suggesting a carry-over effect from their training in the running wheels. Different from our current results, this earlier study showed rCBF to increase in the PFC in both exercise groups compared to quiescent controls. Differences may relate either (i) to differences in functional brain responses in the normal compared to the lesioned brain, (ii) to the effects in the prior study of long-term exercise, or else (iii) to variations in functional brain responses during differing brain mapping paradigms (horizontal treadmill or wheel walking).

In the current study, the skilled compared to the simple task also elicited greater rCBF within the hippocampus (CA1, dentate gyrus). A significant negative functional correlation between the PFC and the posterior hippocampus was noted to a greater extent during the skilled task than during the simple task. Tract tracing has demonstrated that the CA1 region sends prominent efferent projections to the medial PFC (including prelimbic cortex) [25]. Our results suggest that skilled motor training differentially engages the hippocampus, and thus provides another potential point at which different types of exercise may differentially alter memory and learning.

Limitations

Future work with larger numbers of subjects are needed to confirm our findings in this small sample. Furthermore, it is important to remember that while correlation based analyses provide information about functional connectivity, they do not directly address causal relationships. Thus, it is possible that functional connectivity may arise, even in the absence of a direct structural connection through functional linkages across a shared secondary node.

However, while indirect interactions can account for some functional linkages, current evidence suggests that topological parameters are generally conserved between structural and functional networks [26]. Our approach to studying functional connectivity in the rat brain appears reasonable and consistent with the current theoretical understanding of functional connectivity as long as one understands that it does not address causality or directionality of individual connections, and that it is conceivable that covariance between two nodes in a circuit may occur in the absence of their direct structural connectivity.

Our autoradiographic measures of brain functional connectivity were obtained at a single time point. This approach differs from the intra-subject cross correlation analysis often used on functional magnetic resonance imaging (fMRI) time series data. Caution needs to be taken comparing functional connectivity results between different brain imaging modalities (fMRI, positron emission tomography, electroencephalography) and between different analytic methods. Different analytic tools have been adapted to allow the determination of functional associations, either by examining the temporal aspects of time series within subjects or, as in the current study, by modeling the system over the entire experimental period across subjects [27]. While many regions exhibit congruent effects under both analytic approaches [28], in some regions the two analyses can produce divergent results. A current issue of debate remains the advantages and limitations of each analytic method, their applicability to studies of task activation, and their interpretation with regards to neural activity, brain metabolism and cerebral structure [29,30]. Future studies should address the relationship between dynamic neurometabolic coupling and more static measures of regional covariance.

Conclusion

Prelimbic cortex, a medial prefrontal region with features of human dorsolateral PFC [31], plays a significant role in working memory. In rats and mice, lesions of the prefrontal cortex produce significant deficits in spatial working memory tasks such as delayed alternation [32,33], with a possible neuromodulatory role for dopamine D1 receptors [34]. A question raised by our results is whether skilled motor training, which engages the corticostriatal pathway linking the PFC and the dorsomedial striatum can improve, not only motor function, but executive function. Recent studies in human subjects have emphasized the benefits of a wide variety of exercise on cognitive decline related to aging and possibly dementia [1–4]. The mechanisms underlying such improvements remain unknown. Few of these studies have delineated the importance of ‘skill’ as an important exercise parameter that can modulate or restore executive function—a critical component not only for the sequencing of motor actions, but also of cognitive flexibility, reasoning and problem solving, in general.

A necessary ‘next step’ for the field of neurorehabilitation is to move beyond simple recommendations for cardiovascular exercise and resistance training (2008 Physical Activity Guidelines for Americans) [35]. Increasingly it appears that different types of motor training have the potential to differentially induce circuit-specific structural and functional plasticity in the brain. Our current results show that skilled motor activity increases functional connectivity of the PFC, particularly to the dorsomedial sector of the striatum.

Understanding the impact of skilled motor training on the basal ganglia and its related circuitry potentially represents a paradigm shift for the field of neuroplasticity and a new frontier in optimizing neurorehabilitative care.

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References

1. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc.* 2011; 86:876–884. [PubMed: 21878600]
2. Berryman N, Bherer L, Nadeau S, Lauziere S, Lehr L, Bobeuf F, et al. Executive functions, physical fitness and mobility in well-functioning older adults. *Exp Gerontol.* 2013; 48:1402–1409. [PubMed: 24012563]
3. Guiney H, Machado L. Benefits of regular aerobic exercise for executive functioning in healthy populations. *Psychon Bull Rev.* 2013; 20:73–86. [PubMed: 23229442]
4. Voelcker-Rehage C, Niemann C. Structural and functional brain changes related to different types of physical activity across the life span. *Neurosci Biobehav Rev.* 2013; 37:2268–2295. [PubMed: 23399048]
5. Black JE, Isaacs KR, Anderson BJ, Alcantara AA, Greenough WT. Learning causes synaptogenesis, whereas motor activity causes angiogenesis, in cerebellar cortex of adult rats. *Proc Natl Acad Sci U S A.* 1990; 87:5568–5572. [PubMed: 1695380]
6. Remple MS, Bruneau RM, VandenBerg PM, Goertzen C, Kleim JA. Sensitivity of cortical movement representations to motor experience: evidence that skill learning but not strength training induces cortical reorganization. *Behav Brain Res.* 2001; 123:133–141. [PubMed: 11399326]
7. Eggenberger P, Schumacher V, Angst M, Theill N, de Bruin ED. Does multicomponent physical exercise with simultaneous cognitive training boost cognitive performance in older adults? A 6-month randomized controlled trial with a 1-year follow-up. *Clinical interventions in aging.* 2015; 10:1335–1349. [PubMed: 26316729]
8. Eggenberger P, Wolf M, Schumann M, de Bruin ED. Exergame and Balance Training Modulate Prefrontal Brain Activity during Walking and Enhance Executive Function in Older Adults. *Front Aging Neurosci.* 2016; 8:66. [PubMed: 27148041]
9. Voelcker-Rehage C, Godde B, Staudinger UM. Cardiovascular and coordination training differentially improve cognitive performance and neural processing in older adults. *Front Hum Neurosci.* 2011; 5:26. [PubMed: 21441997]
10. Wang Z, Guo Y, Myers KG, Heintz R, Holschneider DP. Recruitment of the prefrontal cortex and cerebellum in Parkinsonian rats following skilled aerobic exercise. *Neurobiol Dis.* 2015; 77:71–87. [PubMed: 25747184]
11. Holschneider DP, Maarek JM, Harimoto J, Yang J, Scremin OU. An implantable bolus infusion pump for use in freely moving, nontethered rats. *Am J Physiol Heart Circ Physiol.* 2002; 283:H1713–1719. [PubMed: 12234827]
12. Sakurada O, Kennedy C, Jehle J, Brown JD, Carbin GL, Sokoloff L. Measurement of local cerebral blood flow with iodo [14C] antipyrine. *Am J Physiol.* 1978; 234:H59–66. [PubMed: 623275]
13. Van Uitert RL, Levy DE. Regional brain blood flow in the conscious gerbil. *Stroke.* 1978; 9:67–72. [PubMed: 341424]
14. Thevenaz P, Ruttimann UE, Unser M. A pyramid approach to subpixel registration based on intensity. *IEEE Trans Image Process.* 1998; 7:27–41. [PubMed: 18267377]
15. Nguyen PT, Holschneider DP, Maarek JM, Yang J, Mandelkern MA. Statistical parametric mapping applied to an autoradiographic study of cerebral activation during treadmill walking in rats. *Neuroimage.* 2004; 23:252–259. [PubMed: 15325372]

16. Friston KJ, Holmes A, Worsley KJ, Poline JB, Frith CD, Frackowiak RS. Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*. 1995; 2:189–210.
17. Wang Z, Pang RD, Hernandez M, Ocampo MA, Holschneider DP. Anxiolytic-like effect of pregabalin on unconditioned fear in the rat: an autoradiographic brain perfusion mapping and functional connectivity study. *Neuroimage*. 2012; 59:4168–4188. [PubMed: 22155030]
18. Paxinos, G., Watson, C. *The Rat Brain in Stereotactic Coordinates*. New York: Elsevier Academic Press; 2007.
19. Brett, M., Anton, J-L., Valabregue, R., Poline, JB. Region of interest analysis using an SPM toolbox. 8th International Conference on functional Mapping of the Human Brain; Sendai, Japan. June, 2002; *NeuroImage*
20. Voorn P, Vanderschuren LJ, Groenewegen HJ, Robbins TW, Pennartz CM. Putting a spin on the dorsal-ventral divide of the striatum. *Trends Neurosci*. 2004; 27:468–474. [PubMed: 15271494]
21. Vaishnavi SN, Vlassenko AG, Rundle MM, Snyder AZ, Mintun MA, Raichle ME. Regional aerobic glycolysis in the human brain. *Proc Natl Acad Sci U S A*. 2010; 107:17757–17762. [PubMed: 20837536]
22. Page KA, Chan O, Arora J, Belfort-Deaguiar R, Dzuira J, Roehmholdt B, et al. Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways. *JAMA*. 2013; 309:63–70. [PubMed: 23280226]
23. Balleine BW, O'Doherty JP. Human and rodent homologues in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology*. 2010; 35:48–69. [PubMed: 19776734]
24. Yin HH, Mulcare SP, Hilario MR, Clouse E, Holloway T, Davis MI, et al. Dynamic reorganization of striatal circuits during the acquisition and consolidation of a skill. *Nat Neurosci*. 2009; 12:333–341. [PubMed: 19198605]
25. Cenquizca LA, Swanson LW. Spatial organization of direct hippocampal field CA1 axonal projections to the rest of the cerebral cortex. *Brain Res Rev*. 2007; 56:1–26. [PubMed: 17559940]
26. Bullmore E, Sporns O. Complex brain networks: graph theoretical analysis of structural and functional systems. *Nat Rev Neurosci*. 2009; 10:186–198. [PubMed: 19190637]
27. Stephan KE. On the role of general system theory for functional neuroimaging. *J Anat*. 2004; 205:443–470. [PubMed: 15610393]
28. Honey CJ, Kotter R, Breakspear M, Sporns O. Network structure of cerebral cortex shapes functional connectivity on multiple time scales. *Proc Natl Acad Sci U S A*. 2007; 104:10240–10245. [PubMed: 17548818]
29. Hutchison RM, Womelsdorf T, Allen EA, Bandettini PA, Calhoun VD, Corbetta M, et al. Dynamic functional connectivity: promise, issues, and interpretations. *Neuroimage*. 2013; 80:360–378. [PubMed: 23707587]
30. Handwerker DA, Ollinger JM, D'Esposito M. Variation of BOLD hemodynamic responses across subjects and brain regions and their effects on statistical analyses. *Neuroimage*. 2004; 21:1639–1651. [PubMed: 15050587]
31. Hoover WB, Vertes RP. Anatomical analysis of afferent projections to the medial prefrontal cortex in the rat. *Brain Struct Funct*. 2007; 212:149–179. [PubMed: 17717690]
32. Jones MW. A comparative review of rodent prefrontal cortex and working memory. *Curr Mol Med*. 2002; 2:639–647. [PubMed: 12420803]
33. Touzani K, Puthanveetil SV, Kandel ER. Consolidation of learning strategies during spatial working memory task requires protein synthesis in the prefrontal cortex. *Proc Natl Acad Sci U S A*. 2007; 104:5632–5637. [PubMed: 17369358]
34. Floresco SB. Prefrontal dopamine and behavioral flexibility: shifting from an “inverted-U” toward a family of functions. *Front Neurosci*. 2013; 7:62. [PubMed: 23626521]
35. Physical Activity Guidelines Advisory Committee. 2008 Physical activity guidelines for Americans. US Dept. of Health & Human Services; Washington, DC: 2008. ODPHP publication no. U0036

Fig. 1. Experimental design

Rats are habituated to the motorized running wheel over 2 days. Thereafter, functional brain mapping occurs during wheel walking in either the complex or the simple wheel with intravenous bolus injection of the perfusion tracer [¹⁴C]-iodoantipyrine. Brains are processed by cryosectioning, autoradiography, whole brain reconstruction of the digitized autoradiograms, followed by voxel-based analysis using statistical parametric mapping.

Fig. 2. Group differences in regional cerebral blood flow of rats during complex wheel walking compared to simple wheel walking compared to the resting condition

Depicted are select coronal slices (anterior-posterior coordinates relative to bregma) of the template brain. Colored overlays show statistically significant increased (red) and decreased (blue) differences ($p < 0.05$ for clusters of >100 contiguous voxels). Right side of the image represents the left side of the brain. Abbreviations: LD (lateral dorsal nucleus of the thalamus), S1FL and S1Tr (primary somatosensory cortex of the forelimb and trunk), VL (ventrolateral nucleus of the thalamus).

Fig. 3.

Seed correlation of left prelimbic cortex (prefrontal cortex, green color) showed that skilled walking increases functional connectivity of the prefrontal cortex $\longleftrightarrow$ striatum. Depicted are select coronal slices (anterior-posterior coordinates relative to bregma) of the template brain. Colored overlays show statistically significant positive (red) and negative (blue) correlation ($p < 0.05$ for clusters of >100 contiguous voxels). Right side of the image represents the left side of the brain.