The dopamine system plays an important role in regulating many brain functions, including the motor function. The blockade of dopamine receptors results in a serious motor dysfunction, such as catalepsy and Parkinsonism. However, the neuronal mechanism underlying the drug-induced motor dysfunction is not well understood. Here, we examine brain-wide activation patterns in Fos-enhanced green fluorescent protein reporter mice that exhibit cataleptic behavior induced by SCH39166, a dopamine D1-like receptor antagonist, and raclopride, a dopamine D2-like receptor antagonist. Support vector classifications showed that the orbital cortex (ORB) and striatum including the caudoputamen (CP) and nucleus accumbens (ACB), prominently contribute to the discrimination between brains of the vehicle-treated and both SCH39166- and raclopride-treated mice. Interregional correlations indicated that the increased functional connectivity of functional networks, including the ORB, CP, and ACB, is the common mechanism underlying SCH39166- and raclopride-induced cataleptic behavior. Moreover, the distinct mechanisms in the SCH39166- and raclopride-induced cataleptic behaviors are the decreased functional connectivity between three areas above and the cortical amygdala, and between three areas above and the anterior cingulate cortex, respectively. Thus, the alterations of functional connectivity in diverse brain regions, including the ORB, provide new insights on the mechanism underlying drug-induced movement disorders.

Key words catalepsy; dopamine; drug-induced parkinsonism; D1 receptor; D2 receptor; Parkinson's disease

INTRODUCTION

Neurological and mental disorders, such as Parkinson’s disease and schizophrenia, have implicated dopaminergic system dysfunction.1,2 Dopamine receptor-targeting drugs are widely used to treat these disorders. Antipsychotics inhibiting dopamine D2-like (D2, D3) receptor signals alleviate positive symptoms in schizophrenia but, at high doses, exhibit serious side effects, such as Parkinsonism and dyskinesia.2,3 In addition to D2-like receptor inhibition, D1-like (D1, D5) receptor inhibition at a high dose also causes catalepsy, which is an immobile state and is similar to Parkinson’s disease symptoms.4 Thus, the prevention of the development of drug-induced movement disorders, including catalepsy and drug-induced Parkinsonism, should be considered when prescribing medications that can inhibit dopamine receptors. Although Parkinson’s disease is characterized by the progressive loss of dopamine neurons in the substantia nigra, the mechanisms of drug-induced parkinsonism still not fully understood.5,6

Dopamine D1- and D2-like receptors are frequently abundant in the caudoputamen (CP) and nucleus accumbens (ACB), with opposite functions, respectively.7,8 Striatal medium spiny neurons, which are divided into D1 receptor- and D2 receptor-expressing neurons, profoundly affect motor function and catalepsy.9,10 Catalepsy occurs in the blockade of dopamine signals in the basal ganglia, medial prefrontal cortex (mPFC), and hippocampus (HIP).11,12 Considering the brain-wide projections of dopaminergic neurons and the expression patterns of dopamine receptors, diverse brain regions may be involved in movement disorders, such as dopamine receptor antagonist-induced catalepsy.5,13 However, the mechanism underlying the drug-induced motor dysfunction when using dopamine D1- and D2-like receptor antagonists have not been well understood.

In the present study, we performed brain-wide neuronal activation mapping at single-cell resolutions of mice exhibiting or not exhibiting cataleptic behavior after exposure to D1 antagonist SCH39166 and D2 antagonist raclopride to investigate the neuronal mechanisms underlying drug-induced cataleptic behavior. A supervised classification and interregional correlation analysis indicated that a diverse functional connectivity, including the orbital cortex (ORB) and the striatum prominently contributes to cataleptic behavior induced by dopamine receptor antagonisms.

MATERIALS AND METHODS

Animals The mice used for behavioral study and for activity mapping were C57BL/6N wild-type mice (SLC, Shizuoka, Japan) and B6.Cg-Tg (Fos-tTA, Fos-EGFP*) 1M may/J
mice (JAX stock #018306; The Jackson Laboratory, Bar Harbor, ME, U.S.A.), which express tetracycline-controlled transactivator and 2-hour half-life enhanced green fluorescent protein (EGFP) directed to activated neurons by the c-fos promoter, respectively. Male mice, aged 8–11 weeks, were used, which were maintained in group housing (3–6 mice per cage) except for singly housed treated mice. They were also kept on a 12-hour light–dark cycle (lights on at 8:00 a.m.) with a controlled room temperature as well as water and food (CMF, Oriental Yeast, Osaka, Japan) available ad libitum. All animal care and handling procedures in mice were approved by the Animal Care and Use Committee of Osaka University (Approval No. 28-1-12). All efforts were made to minimize the number of animals used.

**Drug Administration** Mice received an intraperitoneal injection of the D1/D5 dopamine receptor antagonist SCH39166 (ecopipam; 0.01 or 0.1 mg/kg; Tocris Bioscience, Bristol, U.K.) or the D2/D3 dopamine receptor antagonist raclopride (0.1 or 1 mg/kg; Tocris Bioscience), which were dissolved in saline containing 1% dimethyl sulfoxide (Sigma-Aldrich, St. Louis, MO, U.S.A.).

**Behavioral Procedures** The open-field test (OFT) was performed in a square box (42 × 42 × 30 cm) under 40–50 lx light conditions as previously described. Each mouse was placed in the center of the open field 30 min after drug administration and was allowed to move freely for 10 min. The open field was cleaned using 70% ethanol between each trial. The total locomotor activity was recorded using a video camera (HC-V600M; Panasonic Corp., Osaka, Japan), which was analyzed using the ANY-maze video-tracking software (version 4.99; Stoelting, Wood Dale, IL, U.S.A.).

The bar test was performed with minor modifications, as previously described. A 0.7-cm-diameter steel bar covered with non-slippery tape was 3.5 cm above the bench surface. The catalepsy was measured using the time spent by the mice resting both their front paws on the bar, the duration of which was measured up to a maximum of 1 min. The test was performed 0, 15, 30, 45, and 60 min after drug administration.

**Tissue Preparation for Imaging** Fos-EGFP reporter mice were singly housed at least a week before drug administration. Then, their brains were fixed 2 h 30 min after drug administration. Afterward, they were deeply anesthetized via an intraperitoneal injection of a mixture that contains the following: 3 mg/kg medetomidine (Nippon Zenyaku Kogyo, Fukushima, Japan), 4 mg/kg midazolam (Sandoz Pharma, Basel, Switzerland), and 5 mg/kg butorphanol (Meiji Seika Pharma, Tokyo, Japan). Furthermore, they were transcardially perfused with saline followed by 4% paraformaldehyde (Nacalai Tesque, Kyoto, Japan) dissolved in phosphate-buffered saline (137 mM NaCl, 8.1 mM Na₂HPO₄/12H₂O, 2.7 mM KCl, 1.47 mM KH₂PO₄; pH 7.4). Their brains were excised and immersed in 4% paraformaldehyde dissolved in phosphate-buffered saline until use.

**Whole-Brain Imaging and Brain-Wide Activation Mapping** For serial whole-brain imaging, a block-face serial microscopy tomography (FAST) system was used as previously described. We acquired images in every 5 µm optical section. The x–y plane section images were reconstructed from the field-of-view tiles by overlapping alignment of consecutive sections using an in-house all-in-one stitching program, FASTTitcher, written in Python 3.6. The resulting section images were seamlessly aligned in the z-direction using TRI/FCS-NUC64 software (R.10.00.04.3-3-H-64; Ratoc System Engineering, Tokyo, Japan). The three-dimensional particle recognition detected each EGFP-positive cell, with its spatial coordinates being calculated using TRI/FCS-NUC64 software. Twenty-one brain areas were manually parcellated every 50–100 µm of the stitched images based on morphological features and automatically complemented in the other images using TRI/FCS-NUC64 software.

**Machine Learning Classifier** The number of EGFP-positive cells of each region was transformed into a z-score (average 0 and standard deviation 1 for each region). A support vector classification for the standardized datasets was implemented using the scikit-learn function svm with the linear kernel of the Python library (http://scikit-learn.org/stable/). GridSearchCV in the scikit-learn library was used for hyperparameter optimization.

**Correlation Analysis** The number of EGFP-positive cells of each region was divided by the total number of EGFP-positive cells in each mouse to normalize individual correlation differences. The proportion value was transformed into a z-score. Pearson’s r (Pearson’s correlation coefficient) was calculated using GraphPad Prism 7.04 (GraphPad Software, San Diego, CA, U.S.A.).

**Statistical Analysis** For comparisons among three or more groups where applicable, one-way ANOVA, two-way repeated measures ANOVA, or two-way ANOVA was used. As a post hoc analysis, the Bonferroni multiple comparisons test was used. The difference was considered statistically significant when p < 0.05. Statistical analyses were conducted using GraphPad Prism 7.04 (GraphPad Software).

**RESULTS**

**D1- and D2-Like Receptor Antagonisms Cause Cataleptic Behavior** We first examined the motor abnormalities induced by the blockade of either D1- or D2-like receptors using the OFT and the bar test. As reported earlier, SCH39166 at high-dose 0.1 mg/kg, but not at low-dose 0.01 mg/kg, significantly reduced spontaneous locomotion in the OFT and induced catalepsy in the bar test (Fig. 1A, B). Similarly, raclopride at high-dose 1 mg/kg, but not at low-dose 0.1 mg/kg, significantly reduced spontaneous locomotion in the OFT and induced catalepsy in the bar test (Figs. 1A, B).

**High-Dose D1- and D2-Like Receptor Antagonisms Induce Brain-Wide Neuronal Activation Including the Caudoputamen** To understand the neuronal mechanisms underlying cataleptic behavior induced by dopamine receptor antagonists, we performed the brain-wide mapping of neuronal activation using the Fos-EGFP reporter mice, in which the EGFP expression is driven by the promoter of the immediate early gene c-fos. Fos-EGFP mice brains treated with SCH39166 and raclopride at a low or high dose were imaged using FAST (Fig. 1C). Compared to the neuronal activation in mice brains treated with vehicle, no significant difference is noted with the brains of mice treated with low-dose SCH39166 or raclopride (Fig. 1D). High-dose SCH39166 treatment significantly increased the number of EGFP-positive cells in the somatodendron cortex (MO) and somatosensory cortex (SS) and CP (Fig. 1D). High-dose raclopride treatment also showed neuronal activation in the MO, SS, CP, and HIP (Fig. 1D).
Support Vector Classifiers Identify Different Contributions of Brain Areas Associated with SCH39166- and Raclopride-Induced Cataleptic Behavior

For the unbiased detection of important neuronal responses associated with drug-induced cataleptic behavior, we analyzed the dataset of activation maps by a linear support vector classifier. The top four brain regions with the largest contribution to the classifications are as follows:

(a) Between high-dose SCH39166- and vehicle-treated brains: the CP, auditory cortex (AUD), ACB, and ORB (Fig. 2A).

(b) Between high-dose and low-dose SCH39166-treated brains: the AUD, agranular insular cortex (AI), ORB, and CP (Fig. 2A).

(c) Between high-dose raclopride- and vehicle-treated brains: the ACB, CP, ORB, and lateral septal nucleus (LS) (Fig. 2B).

(d) Between high-dose and low-dose raclopride-treated brains: the CP, ACB, dentate gyrus (DG), and AUD (Fig. 2B).

The brain areas with high-weighted coefficient in both classifications were the ORB, CP, and ACB, implying that neuronal activations in these three areas play key roles in the emergence of drug-induced cataleptic behavior (Fig. 2C).

Interregional Correlations of the ORB, CP, and ACB Are Changed in Mice Exhibiting Cataleptic Behavior

To detect the changes of brain-wide functional connectivity of the ACB, CP, and ORB, we performed an interregional correlation analysis in each group, the correlations of which revealed that Pearson’s correlation coefficients of HIP-ACB were significantly decreased in both brains of high-dose SCH39166- and raclopride-treated mice exhibiting catalepsy (Figs. 3A, B).
difference of Pearson’s correlation coefficients among vehicle-, low-dose, and high-dose SCH39166-treated brains indicated that ORB-LS, ACB-SS, and CP-SS correlations were increased, while ACB- and ORB-cortical amygdala (COA) networks were decreased, in a dose-dose dependent manner (Fig. 3C). In high-dose SCH39166-treated brains, CP-COA and CP-basolateral amygdala (BLA) correlations were decreased. On the other hand, in raclopride-treated brains, ORB-LS, CP-
ACB, and CP-SS correlations were increased, while ACB-, CP-, and ORB-anterior cingulate cortex (ACC) networks were decreased in a dose-dose dependent manner (Fig. 3C), suggesting that the increased functional connectivities of the ORB-LS and CP-SS networks are the common mechanisms underlying D1- and D2-like receptor antagonism-induced cataleptic behavior and that the decreased functional connectivities of the COA networks by D1-like receptor antagonism and of the ACC networks by D2-like receptor antagonism are the distinct mechanisms of the drug-induced cataleptic behavior.

**DISCUSSION**

Medium spiny neurons in the CP and ACB are divided into two distinct groups: D1 receptor-expressing neurons of the direct pathway project to the substantia nigra and D2 receptor-expressing neurons of the indirect pathway project to the medial globus pallidus.\(^7,\text{22}\) Initiation of movements requires the concurrent and coordinated activation of both pathways.\(^23\) As a result, D1 and D2 antagonists cause motor dysfunction. The time difference between cataleptic behaviors induced by D1 and D2 antagonists (Fig. 1) may be due to the difference in their target pathways, direct and indirect pathway. The time difference is also described in the previous study.\(^27\) Since these two pathways control the precise locomotor behavior, the CP and ACB play important roles in dopamine receptor inhibition-induced catalepsy.\(^3,\text{4}\) In this study, we identified the ORB and the CP and ACB as important regions for regulating catalepsy by using whole-brain activation mapping and machine learning (Fig. 2). Although expression levels of D1 and D2 receptor mRNAs in the ORB are lower than that in the CP and ACB, the ORB regulates brain functions, including cognitive function, through interaction with the dopamine system.\(^7,\text{8,24}\) We have previously shown that the ORB is critically involved in hyperlocomotion induced by MK-801, a non-competitive N-methyl-D-aspartate receptor antagonist.\(^25\) Thus, the impaired dopamine system in the ORB may be an underlying mechanism of dopamine receptor antagonist-induced catalepsy.

Dopamine receptor-blocking agents, primarily antipsychotics and antiemetics, cause drug-induced parkinsonism, most commonly when the dose is increased.\(^26,\text{27}\) Drug-induced parkinsonism is also known to be frequently occurred with catatonia.\(^28\) In this study, during high-dose raclopride-induced catalepsy, the interregional correlation of ORB-ACC was reduced, implying that high-dose D2 receptor antagonists may lead to a cortico-cortical network dysfunction (Fig. 3C). The brain state induced by high-dose D2 receptor antagonist is similar to catatonia, which is mainly associated with ORB-prefrontal/parietal cortical dysfunction and abnormal cortico-cortical modulation.\(^29\) In Parkinson's disease, a disruption of the cortical-basal ganglia network involving the dopaminergic direct pathway, not the cortico-cortical network, is noted.\(^5\) Thus, in terms of brain activation, drug-induced movement disorders might be more like catatonia than Parkinsonism.

Atypical dopamine signaling in the striatum, including the CP and ACB, leads to stereotyped repetition and hyperkinetic movements, such as tics.\(^30\) D2 receptor antagonists have been primarily used to treat tic disorders.\(^30\) Although these antagonists have been reported to provide up to 70% tic reduction, they have inadequate responses or intolerable side effects, such as dyskinesia.\(^31,\text{32}\) Our data, showing that both SCH39166 and raclopride commonly changed the neuronal activations in the CP and ACB, suggests that D1 receptor antagonists may also treat tic disorders. In fact, recent clinical study shows that SCH39166, also called ecopipam, reduced tics and were well tolerated.\(^30\) Moreover, the striatum-COA interregional correlation was decreased by SCH39166 treatment, whereas the striatum-ACC interregional correlation was decreased by raclopride (Fig. 3C). The severity of levodopa-induced dyskinesia is correlated to serotonin transporter binding increases in the ventral striatum and ACC, which mediate motor function.\(^33\) Thus, these shown differences in D1- and D2-receptor antagonists on neuronal networks may explain the clinical side effect differences.

In summary, our current findings suggest that impaired cortical-striatal networks are the mechanism underlying the catalepsy induced by dopamine blockade, albeit with differences between D1- and D2-like receptor blockers. In addition, our approach using brain-wide activation mapping combined with hypothesis-free analysis contributes to a better classification of drug-induced movement disorders based on neuronal activation patterns and an achievement of translatable findings between animal models and human diseases.

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**Conflict of Interest** The authors declare no conflict of interest.

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