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SHORT COMMUNICATION
Bilateral overactivation of the sensorimotor cortex in the unilateral rodent model of Parkinson's disease – a functional magnetic resonance imaging study

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Abstract

Functional magnetic resonance imaging (fMRI) is used to investigate the basal ganglia (BG)–cortex circuit using a rat model of Parkinson's disease (PD). The model involves a unilateral destruction of the right substantia nigra by intranigral injection of the dopaminergic neurotoxin 6-hydroxydopamine. Volume of cortical activity was measured by the blood oxygenation level-dependent contrast method while applying electrical forepaw stimulation. The main findings are the following. (i) Contrary to the predictions of the classic model but in line with recent experimental results (positron emission tomography, fMRI and electrophysiology), an increased cortical activity in the sensorimotor cortex of PD rats compared with sham-operated or normal rats was found. (ii) A diffuse neuronal activity at large cortical areas that were not related directly to the stimulation used, was observed. (iii) No difference was found between the lesion and the nonlesion hemispheres when the left or the right forepaw was stimulated; both cortices show significant overactivation of the sensorimotor cortices in addition to diffuse cortical activation. The last finding could be explained by either corticocortical connections or by bilateral BG–cortex connections. These finding suggest that the mutual influence of the two hemispheres is important in the pathophysiology of the BG–cortex circuit and might be crucial in predicting treatments.

Introduction

According to the classic view of the basal ganglia (BG) function in Parkinson's disease (PD) (Albin *et al*., 1989; Bergman *et al*., 1990; DeLong, 1990; Obeso *et al*., 2000), the firing rate of the frontal cortex neurons is reduced due to overactivation of the BG output structures. The reduced frontal cortex activity is believed to produce lower than normal motor activity and akinesia. Using this model, several treatments of PD have been suggested, tested in animals and applied to humans. The basic idea in these treatments is to reduce the inhibition output of the BG and restore the normal cortical activity. These clinical treatments showed improvements of parkinsonian symptoms (Bergman *et al*., 1990; Aziz *et al*., 1991; Limousin *et al*., 1995; Baron *et al*., 2000). In spite of the success of the treatments, there are several aspects that seem to contradict this model (Marsden & Obeso, 1994; Obeso *et al*., 2000). The anticipated reduced cortex activity could explain the disease's akinetic symptoms, but does not support or explain the other two main motor symptoms, namely rigidity and tremor. Naively, these symptoms correspond to over-activation of the cortex as they present overactivation of muscles. Furthermore, previous imaging studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) have shown an increased neuronal activity in different regions of the motor, frontal and sensory cortices in parkinsonian patients (Boecker *et al*., 1999; Sabatini *et al*., 2000). Finally, electrophysiological studies of single neurons in a monkey model of PD reported no change in the mean spontaneous primary motor cortex discharge (Doudet *et al*., 1990; Goldberg *et al*., 2000).

In this study, we aim to use fMRI to further understand the BG–cortex circuit in PD, particularly by testing the contralateral influence between the hemispheres. For this purpose, we use the common rat model for unilateral PD. It involves injection of the catecholamine-selective neurotoxin 6-hydroxydopamine (6-OHDA) directly to the mesencephalic (in the substantia nigra pars compacta) dopamine (DA) area (Bradbury *et al*., 1986; Perese *et al*., 1989; Gerlach & Riederer, 1996; Tolwani *et al*., 1999). We use the blood oxygenation level dependent (BOLD) contrast to measure the cortical response to forepaw stimulation in the normal, sham-operated and PD rats. Surprisingly, we found that our initial hypothesis, namely that the response of the nonlesion hemisphere in a unilateral animal model of PD is normal, does not hold true.

Methods

All surgical and experimental procedures conformed to the Institutional Animal Care and Use Committee guidelines. They were carried out with the approval of the Hebrew University Faculty of Medicine and Hadassah Medical Organization.

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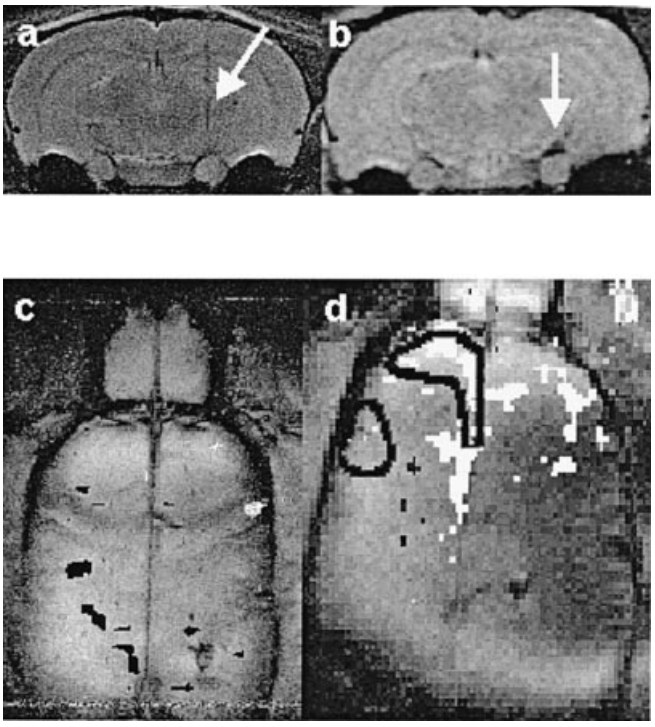

FIG. 1. Anatomical images and activation maps. (a and b) Coronal brain images of two rats at Bregma around –4.8, taken 3 days after injection of 6-hydroxydopamine directly to the substantia nigra (SN). In (a), the cannula track is seen clearly (marked by the arrow). The arrow in (b) marks the SN lesion. In both cases, the lesions are in the right location (dark in these T2*-weighted images). (c and d) Typical BOLD fMRI activation maps (overlaid on axial images) of sham-operated (c) and hemi (right hemisphere) Parkinson's disease (PD) model rats (d). In both cases the left forepaw was stimulated by a current of 1 mA, well below a level that can cause global changes in blood pressure. White areas in the activation maps stands for correlation >0.3, while black areas corresponds to correlation <-0.3. The slice covers most of the rat's cortex with the olfactory bulb on top and the cerebellum (not seen) at bottom. Activation maps were obtained by using the cross-correlation analysis described in Methods. In the PD model rat (d), the activation map shows diffused bilateral overactivation as opposed to the activation map of the sham-operated rat that includes mainly the right motor and sensory cortices. The black lines in (d) illustrate the location of the left hemisphere region of interest (ROI) from which the fraction of activation volume was calculated and the statistics applied. The ROI includes the forepaw motor and sensory areas, as well as the frontal cortex.

Animal models

Forty-five male Sprague–Dawley rats (250–300 g) were used in the study. Of these, 21 were anaesthetized with ketamine (90 mg/kg i.p., Park-Davis, UK) plus xylazine (5 mg/kg i.p., Vitamed, Bat-Yam, Israel) and stereotaxically injected into the right substantia nigra pars compacta with 4 μL 6-OHDA hydrobromide with 0.02% ascorbic acid (NBT; Sigma, Israel), using a 10-μL Hamilton microsyringe fitted with a 26-gauge cannula. The injection rate was 1 μL/min and the cannula was left in place for an additional 5 min.

Lesion coordinates were AP –4.8, ML –1.6, DV –8.4 from dura (Paxinos & Watson, 1982). Seven additional rats went through the same surgical procedure, but were injected with 4 μL of saline (sham-operated rats). The other 17 rats were used as the normal control group. The position and size of the lesion were checked by anatomical MRI a few days after operation and were found to mach the substantia nigra (SN) location. In Fig. 1, we show two examples of this confirmation. Two coronal slices from two rats at Bregma around –4.8 are shown. In Fig. 1a, the needle tract and the lesion are seen clearly, while in Fig. 1b, a larger lesion within the SN is observed. In addition, the rate of rotation after amphetamine (2 mg/kg i.p.) injection was measured 2 weeks after operation in four rats. For all tested rats, the rate of rotation was above 6/min for the first hour (Schwarting & Huston, 1996).

The fMRI measurements were performed 10–14 days after the lesion operation. The rats were anaesthetized with ether just for the restraining in the home-built head and body holder. The fMRI measurements were performed on awake rats to avoid any confounding effects of anaesthesia. Due to the difficulty in completely eliminating motion, careful motion detection procedure was used (discussed later). Out of the 45 tested rats, only 16 were motion-free (seven with lesion, four sham-operated and five normal). For the statistics, only these rats were used. Small needle electrodes were inserted under the skin, into the right and the left forelimbs. The stimulation sequence consists of 0.3 ms rectangular pulses with frequency of 3 Hz. Stimulation amplitude was determined by calculating the mean of the threshold value that causes forelimb motion and the lowest value that causes maximum constriction, for each animal. These values were between 0.75 and 1.0 mA – well below stimulation that can cause global changes in blood pressure (Bock *et al*., 1998). Stimulation sequence was composed of three ON segments (58 s each) with OFF (95 s) intervals in between, plus 186 s of OFF segments at the beginning and the end of the sequence.

MRI method and analysis

MRI measurements were performed on a 4.7 T BioSpec system (Bruker, Karlsruhe, Germany). Radio frequency pulses were transmitted using a 20-mm transmitter/receiver surface coil placed over the skull and centred over the rat midline. For functional studies, the BOLD contrast was used using a gradient echo sequence (TR = 115.4 ms, TE = 40 ms, matrix size = 64×64, FOV = 2.56 cm, two coronal slices ≈ 0.5–2.5 mm DV, 1 mm slice thickness; TR, repetition time; TE, echo time; FOV, field of view; DV, dorsal–ventral). Each dataset consisted of 100 images with temporal resolution of 7.36 s. Anatomical coronal images (TR = 300 ms, TE = 13 ms, matrix size = 256×256, FOV = 2.56 cm, 1 mm slice thickness) were recorded as well.

Image analysis was performed using self-written software, written in IDL (Interactive Data Language, Research Systems, Boulder, CO, USA). The analysis consisted of the following steps. (1) Image reconstruction and denoising. Gaussian noise was filtered out by our semiautomated nonlinear wavelet denoising algorithm (Zaroubi & Goelman, 2000). (2) Motion correction. A motion detection program was applied on each set of images. Each image centre of mass was calculated and compared with the set centre of mass. Images with deviations greater than twice the SD of the set were considered 'with-motion', and were corrected or removed from the dataset. Sets with more than five images with-motion in a row or sets with more than 10% with-motion images were neglected. Afterwards the corrected sets were also inspected manually. (3) Creation of activation maps. All 10 datasets for each animal (five for each stimulated leg) was averaged to improve the signal-to-noise ratio and minimize physiological fluctuations. The averaged sets were cross-correlated with the stimulus temporal pattern using a cross-correlation threshold value of 0.175, which corresponds to $P < 0.05$. Activity was ignored at pixels without a neighbouring pixel above threshold. Activation maps in colour were overlaid on reference images (in black and white) for easier inspection of activity. (4) Choosing regions of interest (ROI). Using the rat brain atlas, two ROIs were defined for further analysis: the right and the left sensorimotor cortices. The ROI includes the

TABLE 1. *P*-values for the region of interest volume of activity comparison (two-tail *t*-test) between sham-operated and 6-hydroxydopamine (6-OHDA)-treated rat groups

Group	Sham-operated vs. 6-OHDA (*P*-value)
Sensorimotor cortex	0.00003
Right sensorimotor cortex	0.00354
Left sensorimotor cortex	0.00013
Right sensorimotor cortex,	
Right forepaw stimulation	0.030
Left forepaw stimulation	0.050
Left sensorimotor cortex,	
Right forepaw stimulation	0.014
Left forepaw stimulation	0.014

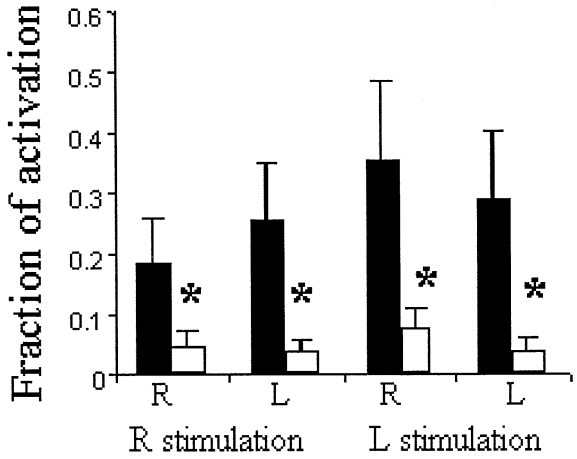

FIG. 2. Comparison of sensorimotor volume of activation between the sham-operated and the Parkinson's disease (PD) model rats groups. The bar diagram shows the average and its standard error of the fraction of activation volume (over the whole region of interest) as calculated by the cross-correlation analysis using a cross-correlation threshold value of 0.175 corresponding to $P < 0.05$. Comparisons were performed in four groups: the right (R) and left (L) sensorimotor cortices subjected to right and left forelimb stimulation. The black bars present the PD model rat group, while the white bars present the sham-operated group. In all four cases, the PD model rats show a significant overactivation over the sham-operated rats.

primary and the secondary motor cortices, the frontal and the sensory cortices (Fig. 1d). To minimize errors in the definition of the ROIs, each ROI was defined five times and the mean ROI was used. (5) Calculating activation volume within the ROIs. Voxels above cross-correlation threshold in each ROI in both slices were counted. This number was normalized to the total volume of the ROI. (6) Performing two-tail *t*-tests between the different groups.

Results

fMRI with BOLD contrast measures changes in the magnetic resonance signal resulting from fluctuations in the ratio of dioxy/oxyhaemoglobin. Recently, it was shown that the BOLD signal is linearly proportional to the local neuronal activity (Heeger *et al*., 2000; Rees *et al*., 2000). We therefore used the BOLD contrast in order to measure the volume of neuronal activity in normal, sham-operated and PD model rats. As expected, no significant difference in cortical activation volume as a response to forepaw stimulation was found between the sham-operated and normal rat groups ($P > 0.5$). Therefore, in the comparison with the lesion rat group discussed later, only the sham-operated group is considered. In Fig. 1c and d, we show an example of the difference in cortical activation of the PD model rat and sham-operated rat resulting from left forepaw stimulation. In addition to the expected activation in the forepaw sensorimotor cortex, the cortical activation of the PD model rat includes areas that are not normally involved in sensory processing. We found that this diffuse appearance is typical for all the PD model rats that have been tested.

To quantify the difference between PD model and sham-operated rats, we calculated the activation volume resulting from forepaw stimulation at specific cortical ROIs and performed statistical comparisons between the groups (Table 1). For illustration we show in Fig. 1d the ROI of the left hemisphere. Volume of activation was defined by the number of voxels above a cross-correlation threshold of 0.175 in the cross-correlation analysis that corresponds to $P < 0.05$ (Methods). Note that this *P*-value defines the significance of the cross-correlation analysis, while the *P*-values in the table correspond to the significance in the comparison between the PD model and sham-operated rat groups. From Table 1, we notice that the volume of cortical activity in the PD model rats is significantly higher than the volume of cortical activity of sham-operated rats in the sensorimotor cortices of both hemispheres, and when the sensorimotor cortex of each hemisphere is compared separately.

To test the differences between the lesioned and nonlesioned hemispheres, we further divide the data into left and right forelimb stimulation. In Fig. 2, the average volume of activation and its standard error over the total selected volume is shown for sham-operated and PD model rat groups. As expected, there is no significant difference in the sham-operated group when either the right or the left forepaw is being stimulated. What is not expected is that the PD rats show similar responses. Although the mean activation volume during left forepaw stimulation is higher than the mean volume during right forepaw stimulation, the difference between these subgroups is not significant. What is also evident from Fig. 2 is the large increase in activation volume in the PD rats: on average an order of magnitude. The calculated *P*-values for the four subgroups shown in Fig. 2 are given in Table 1. All chosen areas show significant overactivation of the PD model rat group, irrelevant of the stimulation side.

Discussion

The classic PD model (Albin *et al*., 1989; Bergman *et al*., 1990; DeLong, 1990; Obeso *et al*., 2000) predicts reduced neuronal activity in cortical motor areas after a SN lesion. In agreement with this classic view, numerous imaging studies using PET have shown cortical hypoactivation in motor-related areas in human PD subjects performing simple motor tasks, compared with normal subjects (Jenkins *et al*., 1992; Playford *et al*., 1992; Jahanshahi *et al*., 1995). Moreover, this deficit cortical activation could be reversed by different treatments aimed at reducing the inhibitory BG output (Jenkins *et al*., 1992; Grafton *et al*., 1995; Limousin *et al*., 1997; Samuel *et al*., 1997; Ceballos-Baumann *et al*., 1999). However, other studies have found different changes in the activity of the sensorimotor cortex, as follows. (1) Single photon emission tomography (Rascol *et al*., 1997) and PET studies on PD patients showed enhanced activation of motor cortical areas after performing

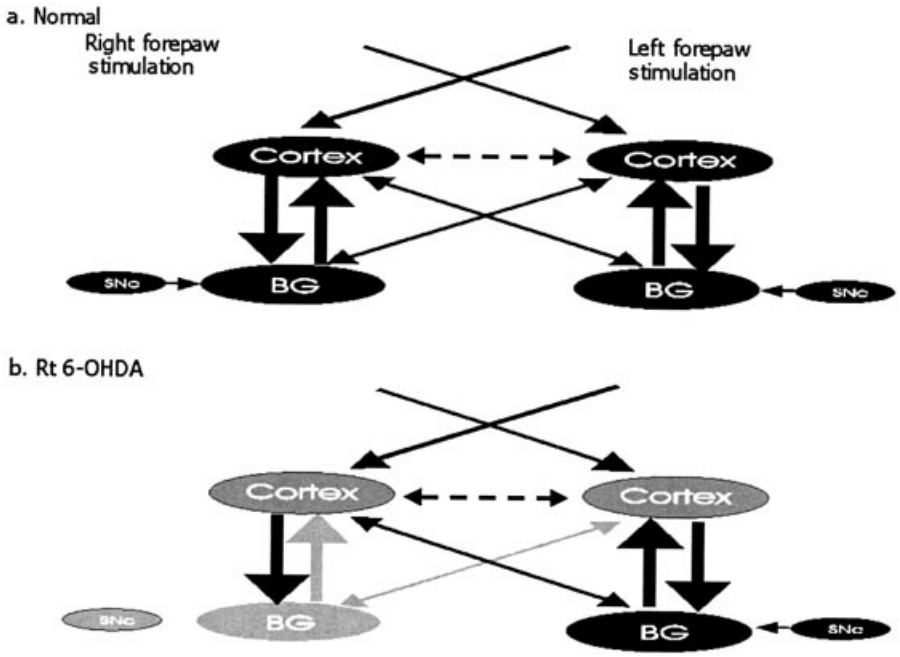

FIG. 3. The suggested reciprocal bilateral basal ganglia (BG)–cortex connections scheme. In addition to the connection between both cortices (not shown) and the ipsilateral connections between the BG and the cortex, the scheme has a two-directional bilateral connection between the BG and the cortex. (a) The scheme under normal conditions and (b) subjected to unilateral substantia nigra pars compacta (SNc) destruction by injection of 6-hydroxydopamine (6-OHDA). During activation of the lesion-side hemisphere, the lesioned BG receives input from its ipsilateral cortex and sends abnormal output to both cortices, resulting in an abnormal response. When the nonlesioned hemisphere is being activated, its cortex sends input to the BG in the two hemispheres. The lesioned BG returns abnormal output to both cortices also causing an abnormal response in both cortices. In both cases, the abnormal output from the lesioned BG causes overactivation of both hemispheres. Note that in the figure, brightness illustrates abnormality.

different motor tasks (Brooks, 1999; Catalan *et al*., 1999) along with enhanced activation of ipsilateral sensory cortical areas following vibratory stimulation tasks (Boecker *et al*., 1999). (2) fMRI studies on PD patients showed bilateral overactivation in the sensorimotor cortex (Sabatini *et al*., 2000). (3) Measurements of the somatosensory-evoked potentials of PD patients showed high-frequency oscillations that are not found in control subjects (Mochizuki *et al*., 1999).

The discrepancy in these finding could be the result of the following: (i) the variety in stimulation paradigms used; (ii) the difficulty of PD patients to perform the motor tasks; (iii) the variance in the severity of the disease in the subjects; and (iv) different ROI used and a possible intercortical compensatory mechanism. For that reason we chose to test cortical activation in the well-defined unilateral PD model rat group using a well-controlled stimulation paradigm.

Recently it was shown that dopamine plays an important role in cortical microcirculation (Krimer *et al*., 1998). This might explain the increase in flow and the fMRI BOLD signal observed in brain regions with high dopamine receptor density following dopamine administration (Chen *et al*., 1997). The alternations in cortical dopamine level resulting from SN lesion could be one of the reasons for these BOLD signal modulations. It was found that dopamine level is reduced in cortical areas in PD patients (Scatton *et al*., 1982, 1983) and in symptomatic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated monkeys (Elsworth *et al*., 1990), but no changes in the D1 and D2 dopamine receptors were found in the unilateral 6-OHDA rat model (Yokoyama & Okamura, 1997; Araki *et al*., 1998). Therefore, our findings are unlikely to be explained by changes in dopamine and dopamine receptor level.

When different classic symptoms of PD patients are being examined, some suggest reduced activity could be anticipated from akinetic symptoms, but others suggest enhanced motor activity, as it is reflected in rigidity and tremor. This complexity is partially observed in the imaging studies mentioned earlier, when along the enhanced overactivation of sensorimotor cortical areas, few other areas are found to show decreased activation. Note that because the volume of activation from the whole ROI is being measured in our analysis, fluctuations in cortical activity within these areas are not observed. This is done to increase measurement statistics due to its higher immunity to ROI selection errors resulting from their larger size. We also note here that in our analysis the average strength of activation is not used but only the volume above a cross-correlation threshold.

In the present study, we aimed to test the bilateral connections between the BG and the cortex, particularly to examine the response of the nonlesion hemisphere to right and left forepaw stimulation. For this reason, we chose to work with a unilateral rat model of PD. Human studies sometimes resembled the unilateral situation. For example, Thobois *et al*. (2000) used PET to study hemiparkinsonic patients. In line with our results, these patients have shown bilateral activation of the motor cortex when the stimulation was given to the akinetic hand. However, a stimulation of the less akinetic hand was not different from control subjects. Even though some of the parkinsonian patients show unilateral symptoms, the DA depletion in the human SN is probably bilateral and both hemispheres are affected. The altered BG activation could affect the cortex differently according to the DA depletion grade. Our data show that, as a consequence of any forepaw stimulation, bilateral activation of the sensorimotor cortex is a frequent phenomenon in both the normal (not shown) and sham-operated rat (Fig. 2) groups. The accepted explanation of this bilateral response is the strong corticocortical connections between the two hemispheres. However, it is somehow

surprising that the bilateral phenomena are retained also in the abnormal activation of the sensorimotor cortex in PD model rats — is it being controlled by the same mechanism or a different one?

Consequently, our finding could be explained in two different ways. First, because both hemispheres are connected strongly through the corpus callosum and other corticocortical connections, the abnormal activity in the lesioned hemisphere affects the nonlesioned hemisphere. Second, the abnormal activity of the nonlesioned hemisphere is explained by contralateral connections between the BG and the cortex. At this point the experimental data cannot reject or support any of these models and future studies are needed to discriminate between the two. The latter approach is illustrated in Fig. 3. In the common view of the BG–cortex circuit, each BG is connected ipsilaterally to the cortex. In line with existing anatomical evidence (Parent & Hazrati, 1995; Gerfen & Wilson, 1996), we suggest an additional reciprocal contralateral connection between the cortex to the contralateral BG. In this case, each cortex sends input to and receives output from both BG.

In summary, we tend to believe that the bilateral BG–cortex connections strongly affect the cortical response, i.e. in the nonlesioned hemisphere these connections are the dominant ones. Furthermore, we anticipate that these connections play an important role in the pathophysiology of PD.

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Abbreviations

6-OHDA, 6-hydroxydopamine; BG, basal ganglia; BOLD, blood oxygenation level dependent; DA, dopamine; fMRI, functional magnetic resonance imaging; PD, Parkinson's disease; PET, positron emission tomography; ROI, region of interest.

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