Pramipexole restores depressed transmission in the ventral hippocampus following MPTP-lesion

Javier Castro-Hernández, Paul A. Adlard & David I. Finkelstein

The hippocampus has a significant association with memory, cognition and emotions. The dopaminergic projections from both the ventral tegmental area and substantia nigra are thought to be involved in hippocampal activity. To date, however, few studies have investigated dopaminergic innervation in the hippocampus or the functional consequences of reduced dopamine in disease models. Further complicating this, the hippocampus exhibits anatomical and functional differentiation along its dorso-ventral axis. In this work we investigated the role of dopamine on hippocampal long term potentiation using D-amphetamine, which stimulates dopamine release, and also examined how a dopaminergic lesion affects the synaptic transmission across the anatomic subdivisions of the hippocampus. Our findings indicate that a 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine induced dopaminergic lesion has time-dependent effects and impacts mainly on the ventral region of the hippocampus, consistent with the density of dopaminergic innervation. Treatment with a preferential D3 receptor agonist pramipexole partly restored normal synaptic transmission and Long-Term Potentiation. These data suggest a new mechanism to explain some of the actions of pramipexole in Parkinson’s disease.
It is likely, therefore, that DA and its regulation may be important in variety of hippocampal functions. This is particularly relevant for conditions such as Parkinson’s Disease which is characterized by the loss/dysfunction of midbrain dopaminergic neurons with associated deficits in fine movement control and motor learning. In the last few years, however, there has been a growing interest in the study of non-motor symptoms such as emotional disturbances and cognitive decline, whose causes have remained largely unknown. Clinical and experimental findings have shown the existence of cognitive decline from early stages, and even before Parkinson’s Disease is diagnosed. Whereas research on non-motor symptoms has mainly focused on frontostriatal functions, several studies in the last 20 years found hippocampal atrophy in Parkinson’s Disease patients, some of which presented with memory impairment. Depression and anxiety, mood disorders which have been related to vHip, are highly prevalent in Parkinson’s Disease patients. A recent cohort study involving a half million people, concluded that there is a direct correlation between depression and the risk of developing Parkinson’s Disease. Despite of the importance of these findings to the quality of life of people living with Parkinson’s Disease and the evidence of the importance of the vHip, little is known about the mechanisms underlying this.

The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a commonly used animal model for parkinsonism. This model causes a degeneration of the dopaminergic system, depleting DA and their metabolites in dorsal striatum and prefrontal cortex. However, due to the difficulty of measuring DA in hippocampus and the question of which region was studied, the effects are controversial. Some studies found no decrease in DA levels after MPTP administration while others showed a depletion after multiple MPTP injections. Despite this uncertainty, MPTP intoxication has been shown to impair several types of memory and also damages synaptic transmission in mice.

In this study we used electrophysiological techniques to investigate how DA pathways modulate hippocampal-dependent functions, using D-amphetamine (Amph) and R-pramipexole (PPX), a dopamine agonist in clinical use in Parkinson’s Disease. We also utilized the MPTP model of Parkinsonism in order to examine the effect of dopaminergic denervation on hippocampal function. We demonstrate that pharmacological elevation of DA with Amph results in an increase in LTP, depression of the Input/Output (I/O) curve and an augmentation in Paired Pulse Facilitation (PPF) ratio under both baseline and MPTP lesion conditions. These effects were consistent across the hippocampus, although larger in vHip than dHip. Moreover, PPX treatment succeeded in restoring the already depressed I/O curve of MPTP-lesioned mice and increased LTP and reduced the PPF ratio in vHip. These findings provide insight into the cognitive deficits and mood disorders that affect Parkinson’s Disease patients and partially explain the antidepressant properties previously described for PPX.

**Results**

**LTP varies between the dorsal and ventral sections of the hippocampus.** To investigate the heterogeneous nature of the hippocampus, we selected sections from the dHip and vHip (Fig. 1A and B).

High frequency stimulation of the Schaffer collateral pathway resulted in larger LTP in dHip than vHip (control dHip, 151% vs. control vHip, 134%, p ≤ 0.0001) (Fig. 1C) when recorded from the proximal stratum radiatum of CA1. This was not accompanied by a change in excitability (I/O curve) (Fig. 1D) or probability of neurotransmitter release (PPF ratio) (Fig. 1E). We chose the 50% of maximum response (S50) to compare the I/O curves in all experiments, since this was the threshold for PPF, baseline and LTP recording.

**Amphetamine effects are more pronounced in ventral hippocampus.** Amphetamine is a highly addictive psychostimulant that mainly acts through the dopamine transporter (DAT), the latter which controls DA reuptake from dopaminergic terminals and can modulate dopaminergic transmission. Amphetamine reverses DAT transport and increases DA release. We were interested in how this DA release modulates synaptic activity in hippocampus. A previous study found that DA caused an inverted-U shape action on cognition, with both low dose and high doses resulting in degraded cognitive responses. Because of this we used two different concentrations (0.1 μM and 10 μM). Our results indicate that Amph evoked an increase in LTP in both the dorsal and ventral hippocampus. When hippocampal sub-regions were analyzed we found that only the lower dose of Amph altered LTP in dHip (control, 151% vs. 0.1 μM Amph, 166%; p ≤ 0.0001; Fig. 2A). Both doses of Amph increased LTP in vHip (control, 134% vs. 0.1 μM Amph, 192%; p ≤ 0.0001; vs. 10 μM Amph, 185%; p ≤ 0.0001; Fig. 2B).

Synaptic excitability is directly determined by the frequency of activation, with excitable synapses producing more and larger action potentials at lower stimulation thresholds. Aberrant excitatory activity of neurons has been described in Parkinson’s Disease. Counterintuitively, previous studies showed that Amph and other psychostimulants depressed the synaptic excitability of some brain structures like VTA and nucleus accumbens (NAc). In concordance with those studies, we found that Amph decreased the synaptic excitability in the hippocampus, but there were different effects along the dorsal and ventral slices. Amph had modest effects in the dHip, the lower dose produced a significant reduction (control, 40% vs. 0.1 μM Amph, 35%; p ≤ 0.05; Fig. 2C). However, vHip exhibited a more pronounced reduction after Amph exposure (control, 41% vs. 0.1 μM Amph, 27%; p ≤ 0.01; vs. 10 μM Amph, 31%; p ≤ 0.05; Fig. 2D and F).

As far as we know, the effect of Amph upon PPF in the different regions of the hippocampus has not been previously studied. However, a previous report showed that Amph increases the PPF ratio in the NAc. Neuromodulators directly regulate the probability of neurotransmitter release from presynaptic boutons by a complex interplay of different presynaptic properties including the ability of altering the size and properties of the vesicle pool, the location of voltage-gated calcium channels at the active zone or the magnitude of calcium influx. The data showed that Amph did not alter the PPF ratio in the dHip (Fig. 2G), but did decrease the probability of neurotransmitter release in the vHip (control PPF ratio, 1.37 vs. 0.1 μM Amph PPF ratio, 1.47; p ≤ 0.05; vs. 10 μM Amph PPF ratio, 1.56; p ≤ 0.01; Fig. 2H).
Figure 1. Electrophysiology experiments using the MEA system to study the differences between dorsal and ventral hippocampus. (A) Scheme of hippocampal dorso-ventral axis, and a slice sample of dorsal and ventral hippocampus placed into a MEA chip. Blue lighted zones were used in our study, avoiding the intermediate level of hippocampus. (B) Representative hippocampal slices from dorsal and ventral subregion. Red (stimulating electrode) and yellow (recording electrodes). Original traces from fEPSP are shown (C) HFS-induced LTP in vHip and dHip (Unpaired t-test, ****p < 0.0001) (D) I/O curve for studying the synaptic excitability differences between dHip and vHip (Unpaired t-test at 50% of maximum stimulation, S50 not significant difference). (E) PPF ratio indicating the probability of neurotransmitter release in dHip and vHip (Unpaired t-test, not significant difference). I/O curves and PPF ratio were recorded before high frequency stimulation.
Figure 2. Effects of D-amphetamine along the dorso-ventral axis in hippocampus. (A) HFS-induced LTP in control dHip vs. 0.1 μM or 10 μM Amph (40 min before recording) (Dunnett’s post hoc test following a one-way ANOVA, *p < 0.0001) (B) HFS-induced LTP in vHip control vs. 0.1 μM or 10 μM Amph (40 min before recording). (Dunnett’s post hoc test following a one-way ANOVA, ****p < 0.0001). (C) I/O curve comparing dHip control vs. 0.1 μM Amph (Unpaired t-test at 50% of maximum stimulation, S50 **p < 0.05). (D) I/O curve comparing vHip control vs. 0.1 μM Amph (Unpaired t-test at 50% of maximum stimulation, S50 **p < 0.01). (E) I/O curve comparing dHip control vs. 10 μM Amph (Unpaired t-test at 50% of maximum stimulation, not significant difference). (F) I/O curve comparing vHip control vs. 10 μM Amph (Unpaired t-test at 50% of maximum stimulation, S50 *p < 0.05). (G) PPF ratio indicating the probability of neurotransmitter release in dHip control vs. 0.1 μM or 10 μM Amph (Dunnett’s post hoc test following a one-way ANOVA, not significant difference). (H) PPF ratio indicating the probability of neurotransmitter release in vHip control vs. 0.1 μM or 10 μM Amph (Dunnett’s post hoc test following a one-way ANOVA, *p < 0.05, **p < 0.01). I/O curves and PPF ratio were recorded before high frequency stimulation.
**PPX** is a preferential D2 receptor agonist. In contrast to the Amph-induced effect on LTP (Fig. 2), PPX enhanced LTP in the dHip (control, 151% vs. 10 μM PPX, 182%; p < 0.0001; Fig. 3A), and vHip (control, 134% vs. 10 μM PPX, 152%; p < 0.0001; Fig. 3B). These data agree with previous published data using a different D2-preferential agonist (7-OH-DETAP)16.

The effects of PPX on synaptic excitability were explored, and found not to alter it in the dHip (Fig. 3C). PPX had the opposite effect when compared with AMPH in the vHip (shown in Fig. 2D and E), evoking a significant increase in synaptic excitability (control, 41% vs. 10 μM PPX, 53%; p ≤ 0.01; Fig. 3D).

Moreover, PPX induced an increase in PPF in the dHip, indicating a decrease in probability of neurotransmitter release (control PPF ratio, 1.29 vs. 10 μM PPX PPF ratio, 1.61; p ≤ 0.0001; Fig. 3E). An increase in I/O curve and reduced PPF was found when PPX was administered to the vHip (control PPF ratio, 1.34 vs. 10 μM PPX PPF ratio, 1.21; p ≤ 0.05; Fig. 3F).

**PMTP lesion triggers an abnormal hippocampal LTP.** We demonstrated that an MTTP nigral lesion increased LTP. When hippocampal sub-regions were separated, the data showed that dHip increased LTP (control, 151% vs. MPTP 60d, 162%; p ≤ 0.01; Fig. 5A). The vHip normally has a greater dopaminergic innervation, 7 days after the MTTP lesion we found enhanced LTP (control, 134% vs. MPTP 7d, 172%; p ≤ 0.0001; Fig. 5B). Sixty days after the MTTP lesion, LTP was still augmented (control, 134% vs. MPTP 60d, 152%; p ≤ 0.0001; Fig. 5B). These data suggest that the reduction of the dopaminergic innervation caused by MTTP lesion results in enhanced LTP, which is only partially reversed by reinnervation. These data suggest that dopamine innervation is required for normal LTP.

To investigate the function of these newly created synapses we explored synaptic excitability (I/O curve) and PPF. Interestingly, we found that MTTP lesion caused a drastic depression in excitability (I/O curve) throughout the whole hippocampus. After 60 days in dHip (control, 40% vs. MPTP 60d, 30%; p ≤ 0.05; Fig. 3C). This excitability gradually decreased over time in the vHip (control, 41% vs. MPTP 7d, 32%; p ≤ 0.001; vs. MPTP 60d, 24%, p ≤ 0.0001, Fig. 3D). Moreover, MTTP lesion increased the PPF in dHip (control PPF ratio, 1.29 vs. MPTP 60d PPF ratio, 1.43; p ≤ 0.05; Fig. 3E) and vHip (control PPF ratio, 1.34 vs. MPTP 7d PPF ratio, 1.95; p ≤ 0.0001; vs. MPTP 60d PPF ratio, 1.51; p ≤ 0.05; Fig. 3F). Taken together these data suggest that even though synaptic remodelling mechanisms are triggered after MTTP lesion, these synapses are not fully functional.

**Amphetamine had opposite effects on LTP in the dorsal and ventral hippocampus after MTTP lesion.** The majority of currently available treatments are aimed at restoring DA levels; the most common of which is the DA precursor, L-Dopa. As it is recognized that excess DA can trigger emotional and cognitive impairments, we examined the effect of elevated DA on LTP in the MTTP-lesioned mouse model.

Amphetamine, which rapidly increases the levels of extracellular dopamine, caused opposite effects along the dorso-ventral hippocampal axis of MTTP-lesioned mice. Specifically, there was a reduction of LTP in the dHip (MPTP 60d control, 162% vs. MPTP 60d + 0.1 μM Amph, 147%; p ≤ 0.05; vs. MPTP 60d + 10 μM Amph 119%; p ≤ 0.0001; Fig. 5A) and an enhancement of LTP in the vHip (MPTP 60d 152% vs. MPTP 60d + 0.1 μM Amph, 192%; p < 0.0001; Fig. 6B), the latter which is consistent with the dopaminergic terminal reinnervation shown in Fig. 4C. The main reason to perform the 7 day experiment after MTTP experiments was to check if the ampheta-mine-induced increase of LTP that we found in vH after 60 days of MTTP lesion was in response to the reinnervation and plasticity of the vH. Amphetamine did not induce any augmentation of LTP after 7 days in the vHip, (MPTP 7d control, 172% vs. MPTP 7d + 0.1 μM Amph, 164%; Fig. 6B). This data suggests that a reinnervation of hippocampus happened, partially recovering the ability for amphetamine to induce LTP.

Amphetamine could not further decrease the already depressed excitability of MTTP-lesioned mice in dHip (MPTP 60d control, 30% vs. MPTP 60d + 0.1 μM Amph, 32% vs. MPTP 60d + 10 Amf, 31%; not significant; Fig. 6C). However, Amph caused an increase in I/O curve of 155% after 7 days of MTTP lesion in the vHip (MPTP 7d control 31% vs. MPTP 7d + 0.1 μM Amph, 48%; p ≤ 0.0001; Fig. 6D). After 60 days, the higher dose of Amf produced a decrease (−21%) the suppressed I/O curve excitability in vHip (MPTP 60d control, 24% vs. MPTP 60d + 10 μM Amf, 19%; p ≤ 0.01; Fig. 6E), but the lower dose had no significant effect (MPTP 60d control, 24% vs. MPTP 60d + 10 μM Amf 22%; not significant; Fig. 6E).

Analysis of the PPF ratio indicated that only the higher doses of Amf increased the evoked potential in the dHip 60 days following MTTP lesion (MPTP 60d control PPF ratio, 1.43 vs. MPTP 60d + 0.1 μM Amf PPF ratio, 1.41 vs. MPTP 60d + 10 μM Amf PPF ratio, 1.31; p ≤ 0.05; Fig. 6F). In accordance with the change in I/O curve excitability, Amf produced a decrease in the PPF ratio in the vHip 7 days after MTTP lesion (MPTP 7d control PPF ratio, 1.48 vs. MPTP 7d + 0.1 μM Amf PPF ratio, 1.23, p ≤ 0.0001; Fig. 6G), but there were no changes in PPF ratio after 60 days indicating partial restoration of function (MPTP 60d control PPF ratio, 1.51 vs. MPTP 60d + 0.1 μM Amf PPF ratio, 1.44 vs. MPTP 60d + 10 μM Amf PPF ratio, 1.39; not significant; Fig. 6H).
Figure 3. The effects of R-pramipexole treatment along the dorso-ventral axis in hippocampus. (A) HFS-induced LTP in dHip control vs. 10μM PPX (40 min before recording) (Unpaired t-test, ****p < 0.0001). (B) HFS-induced LTP in vHip control vs. 10μM PPX (40 min before recording) (Unpaired t-test, ****p < 0.0001). (C) I/O curve comparing dHip control vs. 10μM PPX (Unpaired t-test at 50% of maximum stimulation, not significant difference). (D) I/O curve comparing vHip control vs. 10μM PPX (Unpaired t-test at 50% of maximum stimulation, S50 **p < 0.01). (E) PPF ratio indicating the probability of neurotransmitter release in dHip control vs. after 10μM (Unpaired t-test, ****p < 0.0001). (F) PPF ratio indicating the probability of neurotransmitter release in vHip control vs. after 10μM PPX (Unpaired t-test, ****p < 0.0001). I/O curves and PPF ratio were recorded before high frequency stimulation.
Pramipexole enhances the synaptic transmission in ventral hippocampus of MPTP-lesioned mice. Recently published data concluded that PPX improves depression-like symptoms in Parkinson's Disease\(^3\) and in animal models\(^4\). However, the mechanisms involved have not been well characterized. Our data showed that PPX evoked an augmentation of LTP only in vHip (MPTP 60d control, 152% vs. MPTP 60d + 10\(\mu\)M PPX; 182%; \(p \leq 0.0001\); Fig. 7B), with no effect in dHip (MPTP 60d control, 163% vs. MPTP 60d + 10\(\mu\)M PPX, 164%, not significant; Fig. 7A).

PPX did not affect excitability of PPF in dHip (MPTP 60d control, 30% vs. MPTP 60d + 10\(\mu\)M PPX, 32%; Fig. 7C), and evoked potential of PPF as shown in Fig. 7E (MPTP 60d control PPF ratio, 1.43 vs. MPTP 60d + 10\(\mu\)M PPX PPF ratio, 1.64; \(p \leq 0.01\)). In contrast, PPX largely recovered the I/O curve excitability that had been depressed by MPTP lesion by up to 80% of normal value in vHip (MPTP 60d control, 24% vs. MPTP 60d + 10\(\mu\)M PPX 33%, \(p \leq 0.001\); Fig. 7D) and decreased the PPF in the vHip hippocampal sub-region (MPTP 60d control PPF ratio, 1.51 vs. MPTP 60d + 10\(\mu\)M PPX PPF ratio, 1.32; \(p \leq 0.01\); Fig. 7F). These data suggest that PPX has a postsynaptic site of action as well as a possible therapeutic benefit in the reformed synapses.

Discussion

In this study we investigated the role of dopaminergic pathways in the function of the dorsal and ventral hippocampus. These results confirm that the dopaminergic system is a key regulator of normal hippocampal function and the MPTP data suggests that the dopaminergic lesion has different effects on synaptic transmission along the dorso-ventral axis in the hippocampus, having more profound effects on the vHip where there is a larger dopaminergic innervation\(^1\). Furthermore, the MPTP lesion resulted in time-dependent changes in dopamine: a short-term dopaminergic denervation and longer-term compensatory mechanisms that resulted in dysfunctional synapses\(^1\).

Our results confirm that there is a differential capability to induce LTP across the dorso-ventral hippocampal axis. In agreement with these results we found that under normal conditions, LTP is larger in the dHip than vHip.
Figure 5. Electrophysiology experiments using MEA System to study the effects of short- and long-term MPTP lesion across the dorso-ventral axis in hippocampus. (A) HFS-induced LTP in dHip control vs. after 60 days of MPTP lesion (Unpaired t-test, **p < 0.01). (B) HFS-induced LTP in vHip control vs. after either 7 days or 60 days after MPTP lesion (Dunnett’s post hoc test following a one-way ANOVA, ****p < 0.0001). (C) I/O curve comparing dHip control vs. after 60 days of MPTP lesion (Unpaired t-test at 50% of maximum stimulation, S_{50} *p < 0.05). (D) I/O curve comparing vHip control vs. after either 7 days or 60 days of MPTP lesion (Dunnett’s post hoc test following a one-way ANOVA, ***p < 0.001, ****p < 0.0001). (E) PPF ratio indicating the probability of neurotransmitter release in dHip control vs. after 60 days of MPTP lesion (Unpaired t-test, *p < 0.05). (F) PPF ratio indicating the probability of neurotransmitter release in vHip control vs. after either 7 days or 60 days of MPTP lesion (Dunnett’s post hoc test following a one-way ANOVA, ****p < 0.0001, *p < 0.05). I/O curves and PPF ratio were recorded before high frequency stimulation.
Figure 6. The effects of D-amphetamine on hippocampal synaptic plasticity of short- and long-term MPTP-lesioned mouse. (A) HFS-induced LTP in dHip vs. MPTP 60d (Unpaired t-test, ***p < 0.001). dHip MPTP 60d vs. MPTP 60d 0.1 μM or 10 μM Amph (Dunnett’s post hoc test following a one-way ANOVA, *p < 0.05, **p < 0.01, ****p < 0.0001). (B) HFS-induced LTP in vHip vs. MPTP 7d (Unpaired t-test, ****p < 0.0001). vHip MPTP 7d vs. MPTP 7d 0.1 μM Amph (Unpaired t-test, not significant difference), vHip MPTP 60d vs. MPTP 60d 0.1 μM or 10 μM Amph (Dunnett’s post hoc test following a one-way ANOVA, ****p < 0.0001). (C) I/O curve dHip vs. MPTP 60d (Unpaired t-test at S50, not shown). dHip MPTP 60d vs. MPTP 60d 0.1 μM or 10 μM.
Amph (Dunnett’s post hoc test following a one-way ANOVA, not significant). (D) vHip vs. MPTP 7d (Unpaired t-test, S90 repeated data shown in Fig. 5.), vHip MPTP 7d vs. MPTP 7d 0.1μM Amph (Unpaired t-test at S90, not significant). vHip MPTP 7d vs. MPTP 7d 0.1μM Amph (Unpaired t-test at S90, not significant). vHip MPTP 60d vs. MPTP 60d 0.1μM or 10μM Amph (Dunnett’s post hoc test following a one-way ANOVA, not significant difference). (E) I/O curve comparing vHip vs. MPTP 60d (Unpaired t-test at S90, repeated data shown in Fig. 5). vHip MPTP 60d vs. MPTP 60d 0.1μM or 10μM Amph (Dunnett’s post hoc test following a one-way ANOVA, *p < 0.05). (F) PPF ratio in dHip vs. MPTP 60d (Unpaired t-test, *p < 0.05). dHip MPTP 60d vs. MPTP 60d 0.1μM or 10μM Amph (Dunnett’s post hoc test following a one-way ANOVA, *p < 0.05). (G) PPF ratio in vHip vs. MPTP 7d (Unpaired t-test, **p < 0.0001). vHip MPTP 7d vs. MPTP 7d 0.1μM Amph (Unpaired t-test, ****p < 0.0001). (H) PPF ratio in vHip vs. MPTP 60d (Unpaired t-test, *p < 0.05). vHip MPTP 60d vs. MPTP 60d 0.1μM or 10μM Amph (Dunnett’s post hoc test following a one-way ANOVA, not significant difference). I/O curves and PPF ratio were recorded before high frequency stimulation.

as have been described previously37. This phenomenon can be partly explained by differences in density of dopaminergic innervation along the hippocampal dorso-ventral axis14. The question of how this difference could be influenced in a pathological condition such as Parkinson’s Disease however, has yet to be answered. To address this question, we used a neurotoxin (MPTP) that preferentially causes a degeneration of dopaminergic neurons. We were interested in the short-term, but also particularly in the long-term effects of the lesion as this is more comparable to the type of chronic degeneration and compensatory repair that characterizes Parkinson’s Disease. We hypothesize that under normal conditions the dopaminergic innervation suppresses hippocampal excitability and LTP. During the course of Parkinson’s Disease the altered dopaminergic innervation results in hippocampal dysfunction and may partially explain some of the enhanced neuropsychiatric manifestations that occur in the disease. We found a distinct increase in LTP along the dorso-ventral hippocampal axis that corroborated our hypothesis. However, following MPTP lesion, the enhancement of LTP was more pronounced in vHip than dHip, coincident with the proportions of dopaminergic innervation. Interestingly, LTP induction after MPTP lesion was time-course dependent. Seven days after MPTP lesion, we found a robust increase in LTP in the vHip and the largest dopaminergic denervation. At 60 days post-MPTP lesion, LTP was still larger than control in both vHip and dHip, but downregulated compared with the short-term lesion in vHip. This moderation of LTP occurred in parallel with the dopaminergic reinnervation of vHip (Fig. 8). Also, we found that MPTP lesion caused a time-dependent depression in synaptic excitability, as indicated by alterations in PPF and the I/O curve. Recent works suggesting that a dopaminergic lesion could potentiate GABA inhibition could explain this phenomenon, but further experiments are needed38.

A theoretical model explains LTP as a mechanism for short term modification of the synapse and a longer term mechanism for stimulating spine formation3. Glutamate release is required to induce LTP, and induces de novo growth of functional spines11. Dopamine release from the VTA and SN inputs to the hippocampus are required for LTP at Schaffer collateral synapses where it controls the excitability of CA1 pyramidal neurons through direct modulation of GABAergic interneuron excitation39.

Moreover, it has been demonstrated that the late phase of hippocampal LTP (after 60 min of HFS) can be blocked in presence of D1 antagonists or D1 KO mice40–44. Although studies about synaptic transmission in hippocampus following MPTP lesion did not find significant differences of LTP from longer time of 30 min. post HFS or TBS45–47, further studies are needed to check whether our results are only related to the short phase of LTP.

We suggest a model (Fig. 8) where a short-term lesion causes an enhanced LTP as direct result of the loss of dopamine innervation23. There is a discordance amongst the studies that have examined LTP following MPTP lesion, which is most likely caused by different experimental approaches e.g. varying timeframes post-MPTP, different schedule of MPTP treatment, different protocol to induce LTP and different origins/orientations of the slices along the dorso-ventral axis of the hippocampus23,24,46. No previous studies have differentiated between dHip and vHip24–47. Further other studies found an enhancement of fEPSP when MPTP was applied to the hippocampus in the bath23. The theoretical model explains LTP as a mechanism for short modification of the synapse and in the longer term a mechanism for stimulating spine formation. Other authors have found enhanced LTP induced by an injury. Injury of visual cortex is followed by processes of enhanced neuroplasticity like LTP49. Other studies found an increase in LTP was observed after closed head injury in hippocampal CA150. These data support the view that a compensatory mechanism for LTP or a mechanism of remodeling the neuronal networks is plausible following injury. Our results indicate that function is gradually and only partially restored in 60 days when the hippocampal DA networks are gradually recovered. This suggests that these newly formed terminals only partially conserve the normal function of DA networks, and this could be aided by using drugs that modulate dopaminergic actions (Amph-like or PPX).

Amphetamine is a commonly used cognitive enhancer prescribed for attention-deficit hyperactivity disorder (ADHD). It is known that Amph promotes LTP in CA1 region of the hippocampus51. Whilst the cellular response to Amph depends on the level of DAT expression, with its activity and potency varying across striatal sub-regions52, the mechanisms underlying the differential effects of Amph in the hippocampus has yet to be clarified. Therefore, we sought to determine whether Amph had a larger effect in vHip because of the larger dopaminergic innervation or a because of differential effects on cathecolamines and serotonin53. Our data indicate that Amph enhances LTP in the whole hippocampus, but its potency varies along the dorso-ventral axis, with the vHip showing the largest increase in LTP. Also, we found that Amph depressed the synaptic excitability in the vHip, as previously described in NAc28 and VTA27. Moreover, Amph increased the PPF in the vHip, similar to that shown...
Figure 7. The effects of PPX on hippocampal synaptic plasticity of long-term MPTP-lesioned mouse. (A) HFS-induced LTP in dHip control vs. after 60 days of MPTP lesion (Unpaired t-test, **p < 0.01). dHip after 60 days of MPTP lesion vs. after 60 days of MPTP lesion treated with 10μM PPX (Unpaired t-test, not significant difference). (B) HFS-induced LTP in vHip control vs. after 60 days of MPTP lesion (Unpaired t-test, ****p < 0.0001). vHip after 60 days of MPTP lesion vs. after 60 days of MPTP lesion treated with 10μM PPX (Unpaired t-test, ****p < 0.0001). (C) I/O curve comparing dHip control vs. after 60 days of MPTP lesion (Unpaired t-test at 50% of maximum stimulation, S50 data shown in Fig. 3). I/O curve comparing dHip after
agonist (PD 128907)54, although they did not separate slices along the dorso-ventral axis and our data indicate and emotional alterations found in individuals treated with L-Dopa12. It is reasoned that Amph is acting as a DA lesion, when the dopaminergic innervation is partly restored, Amph did recover its ability to inducing LTP. This data indicate that the dopaminergic system is crucial for low dose Amph-mediated LTP induction in the vHip. The observation that Amph caused a decrease in LTP in the dHip of MPTP-lesioned mice may explain cognitive and emotional alterations found in individuals treated with L-Dopa12. It is reasoned that Amph is acting as a DA releaser, increasing DA in the synaptic cleft to give the same functional result as current dopamine therapeutics.

We want to emphasise an apparent parallelism between MPTP and Amph-induced LTP, where in both treatments synaptic excitability was depressed and PPF was increased in vHip.

We also examined the effects of PPX, a D3-preferent agonist, which was found to increase LTP in the hippocampus in a similar manner to that shown with another D3 dopamine receptor agonist (7-OH-DPAT)16. The differences with Amph are possibly due to D3R being expressed not only in the presynaptic dopaminergic neurons, but also in the postsynaptic neuron where it modulates GABAergic transmission44. However, further experiments using KO mice or antagonists are needed to check whether this effect is D3R-mediated. We also found that PPX evoked a disinhibition in vHip, as demonstrated by either a decrease in PPF ratio or by an increase in the synaptic excitability (I/O curve). Hammad and Wagner described this phenomenon using another D3 dopamine receptor agonist (PD 128907)55, although they did not separate slices along the dorso-ventral axis and our data indicate that this effect is vHip specific. This disinhibitory ability of PPX led us to question whether PPX could restore normal hippocampal function in MPTP-lesioned mice. Our results indicate that PPX succeeded, not only increasing the I/O curve and decreasing the PPF of MPTP-lesioned mice, but increasing the LTP in vHip. These data add a new mechanism of action for PPX, and could partly explain the antidepressant effects described for PPX in both Parkinson’s Disease33 and models of Parkinsonism55. Moreover, we propose a possible mechanism that could be considered to counteract the depressing effect caused by Amph and other psychostimulants27,28. However, whether this disinhibitory effect of PPX in the vHip could be used for restoring the depressed excitability induced by Amph and its impact over drug addiction should be further explored. Also, regarding to the mechanism of action of PPX, experimental studies carried out over the last two decades indicate that D3R agonists can mediate their neuroprotective effects through D3R-dependent and D3R-independent mechanisms56,57. Therefore, further experiments would be needed to fully characterize all the dopaminergic receptors action in these models.

Our findings shed light on the role of dopaminergic system on hippocampal function, and particularly could help for the better understanding of the sequential mood changes associated with Parkinson’s Disease. The main findings are: 1) the dopaminergic system has a prominent effect on the synaptic activity in vHip but lesser in the dHip; 2) The discovery of a differential susceptibility to dopaminergic MPTP lesion across the dorso-ventral axis in hippocampus. These lesions have distinct acute and chronic effects; 3) We propose a novel mechanism of PPX evoked a disinhibition in vHip, as demonstrated by either a decrease in PPF ratio or by an increase in the synaptic excitability (I/O curve). Hammad and Wagner described this phenomenon using another D3 dopamine receptor agonist (PD 128907)55, although they did not separate slices along the dorso-ventral axis and our data indicate that this effect is vHip specific. This disinhibitory ability of PPX led us to question whether PPX could restore normal hippocampal function in MPTP-lesioned mice. Our results indicate that PPX succeeded, not only increasing the I/O curve and decreasing the PPF of MPTP-lesioned mice, but increasing the LTP in vHip. These data add a new mechanism of action for PPX, and could partly explain the antidepressant effects described for PPX in both Parkinson’s Disease33 and models of Parkinsonism55. Moreover, we propose a possible mechanism that could be considered to counteract the depressing effect caused by Amph and other psychostimulants27,28. However, whether this disinhibitory effect of PPX in the vHip could be used for restoring the depressed excitability induced by Amph and its impact over drug addiction should be further explored. Also, regarding to the mechanism of action of PPX, experimental studies carried out over the last two decades indicate that D3R agonists can mediate their neuroprotective effects through D3R-dependent and D3R-independent mechanisms56,57. Therefore, further experiments would be needed to fully characterize all the dopaminergic receptors action in these models.

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Methods

Animals. Male C57BL/6J mice aged 11 weeks weighing between 20 and 25 g were used for this study. All procedures involving mice conformed to the Australian National Health and Medical Research Council code of practice for the care and use of animals for scientific purposes and were approved by the Florey Institute animal ethics committee. All experiments were designed to minimize the number of animals used, pain and discomfort.

MPTP Intoxication protocols. C57BL/6J mice were administered MPTP (Sigma, USA) in an acute dosing regimen of 60 mg/Kg given over four injections (15 mg/Kg each) 2 hours apart58. Each experimental trial contained MPTP-lesioned animals that were randomly subdivided into a sham group and MPTP lesion group. Experimenters were blinded to the assignment for each of the groups. After either 7 or 60 days post-MPTP administration, mice were either culled and brains collected for LTP or they were deeply anaesthetized and

60 days of MPTP lesion vs. after 60 days of MPTP lesion treated with 10μM PPX (Unpaired t-test, not significant difference). (D) I/O curve comparing vHip control vs. after 60 days of MPTP lesion (Unpaired t-test at 50% of maximum stimulation, S90 data shown in Fig. 3). I/O curve comparing vHip after 60 days of MPTP lesion vs. after 60 days of MPTP lesion treated with 10μM PPX (Unpaired t-test, **p < 0.001). (E) PPF ratio indicating the probability of neurotransmitter release in dHip control vs. after 60 days of MPTP lesion (Unpaired t-test, *p < 0.05). PPF ratio indicating the probability of neurotransmitter release in dHip control vs. dHip after 60 days of MPTP lesion treated with 10μM PPX (Unpaired t-test, **p < 0.01). (F) PPF ratio indicating the probability of neurotransmitter release in vHip control vs. vHip after 60 days of MPTP lesion (Unpaired t-test, *p < 0.05). PPF ratio indicating the probability of neurotransmitter release in vHip control vs. vHip after 60 days of MPTP lesion treated with 10μM PPX (Unpaired t-test, **p < 0.01).
tissues collected for either western blot or stereology. The size of the lesion was assessed using stereology. The total number of DA neurons in the SNpc was estimated using a fractionator sampling design. Counts were made at regular predetermined intervals (x = 140 μm, y = 140 μm). Systematic samples of the area occupied by the nuclei were made from a random starting point. An unbiased counting frame of known area (45 μm × 35 μm) was superimposed on the image of the tissue sections using stereology software (MBF, Stereo Investigator) utilizing a 63x objective lens (Leica, N.A. 1.36). Experimenters were blinded to the treatments of each of the groups. The dopamine axonal innervation of the dorsal striatum was assessed by measuring the densitometry of TH immunoreactivity using Image J (v 1.49, NIH).

Microelectrode array electrophysiology. We study synaptic activity parameters such as; The I/O curve and PPF. The majority of hippocampal synapses terminate on dendrites that integrate with multiple inputs that compute to produce an output (field excitatory postsynaptic potential, fEPSP). I/O curve serves as an index of synaptic excitability of large neuronal populations. PPF ratio (fEPSP2/fEPSP1) is used as an easy measure of the probability of neurotransmitter release, where an increase of PPF ratio is interpreted as a decrease of probability of neurotransmitter release, and vice versa.

The animals were killed and brain removed. The brain was cut into 300 μm Horizontal sections with a vibrotome (Leica VT1200S) according to the lamellar orientation of hippocampus. We chose slices belonging to dHip, that serves cognitive function, and the vHip that corresponds to the affective hippocampus. Intermediate slices were discarded as it has partly overlapping characteristics with its neighbours (see Fig. 1A). After sectioning, ventral or dorsal hippocampal slices were pre-incubated for 40 min at 34˚C with either D-amphetamine (0.1 μM or 10 μM; Sigma, USA, pramipexole (10 μM; Sigma) in carbogen bubbled aCSF solution, or carbogenated aCSF solution alone (control).

One acute hippocampal slice was transferred from slice-holding container (60 min pre-incubation in carboxenated aCSF at 34˚C) to a 3D-MEA chip with 60 electrodes spaced 200 μm apart (60 MEA 200/30 iR-Ti: MCS GmbH, Reutlingen, Germany). The slice was immobilized with a harp grid (ALA Scientific Instruments, New York, USA) and was continuously perfused with carbogenated aCSF (3 ml/min at 32˚C). The Schaffer-collateral pathway was stimulated by injecting a biphasic current waveform (100 μA) through one selected electrode at 0.033 Hz. Care was taken to choose the stimulating electrode in the same region from one slice to the other. The peak-to-peak amplitude of fEPSP at the proximal stratum radiatum of CA1 was analyzed using LTP-Analyzer (MCS GmbH, Reutlingen, Germany). Following a 20 min incubation period, slices were continuously stimulated with medium-strength stimuli. When stable evoked fEPSPs were detected (after at least 20 min), the stimulus threshold was determined, and a stimulus strength-evoked response curve (i.e. input-output, stimulation voltage vs evoked response amplitude) was recorded by gradually increasing stimulus intensity until the maximal fEPSP

Figure 8. The triad: Dopamine, Glutamate and Spines Glutamatergic and DA terminals converge at a number of targets, including the frontal cortex, amygdala, NAc, dorsal and ventral striatum and hippocampus. Glutamatergic terminals are located, like caps, on the tops of the spines and the DA terminals synapse on the neck of the spines. Regulation of this synaptic organization is now considered pivotal in understanding the synaptic plasticity that underpins CPu dysfunction in addiction and Parkinson’s disease. However, these specialized structures have been poorly studied in hippocampus, where a recent study suggests that DA terminals also directly control GABA inhibitory interneurons. Our data and other studies suggest that, DA indirectly modulates pyramidal neurons activity. We propose that seven days after MPTP dopaminergic terminal loss disrupted synaptic transmission, as the I/O curve decreased and PPF increased. After sixty days of lesion, LTP was downregulated by the newly innervated synapses. However, the synaptic activity was not fully restored. PPX succeeded on restoring the impaired synaptic transmission, and increasing LTP in MPTP-lesioned mouse.
(peak amplitude of fEPSPs was appeared) was obtained. Only electrodes showing PPF were chosen for LTP stimulation and recording. The intensity of the test stimulus was set to be 50% of the threshold (S2). After recording at least 30 min of stable baseline fEPSPs (baseline control sequence), LTP was induced by applying 3 bursts of high frequency electrical stimuli: 3 × 100 Hz, 500ms width with 20s interval at the tested stimulation intensity, then fEPSPs were recorded for 30 min. For illustration purposes a 10 min interval from the tetanus, has not been displayed or used in the calculation of LTP. We have only shown the LTP response once stabilized. 20 to 80% of peak amplitude of the initial portion of fEPSP was analyzed (LTP data are expressed as % of fEPSPs over the baseline). After LTP recording, PPF (PPF2) was registered again in order to check the health of the slices (data not shown). PPF ratio was calculated by dividing the second peak of fEPSP amplitude by the first peak of fEPSP amplitude.

**Immunohistochemistry for Tyrosine Hydroxylase.** In a different group of mice 30 μm horizontal sections were cut with a cryostat (Leica, Germany), collected in parallel series, and immersed for 30 minutes in 3% H2O2 to inactivate endogenous peroxidase, and incubated for 60 minutes at room temperature in 4% normal goat serum (NGS; Jackson ImmunoResearch, West Grove, PA) in PBS, containing 0.05% Triton X-100 (TX-100; Sigma), and overnight in PBS containing 2% NGS and rabbit anti-TH polyclonal antibody (1:3000; Millipore, USA). After several rinses, the sections were incubated for 2 hours in biotinylated rabbit anti-goat antiserum (1:300; Sigma), and 1:200 NGS in PBS. Immunoreactions were visible after incubation for 1 hour at RT in ExtrAvidin–peroxidase (1:1500; Sigma) in PBS, and after 5 minutes in 0.005% 3′-3′-diamobenzidine tetrachloride (DAB; Sigma) and 0.001% H2O2 in cacodylate buffer 0.05 N pH 7.6. After several rinses, sections were mounted on gelatinized slides, dehydrated, coverslipped with DePeX and photographed with a Leica microscope (Leica, N.A. 1.36).

**Western-blot for Tyrosine Hydroxylase.** Western blot was used to investigate protein expression of TH (1:10,000; Millipore), Samples were electrophoresed in a Bolt system using 4–12% Bis-Tris Plus 10 well gels (Thermo–Fisher, USA).

**Statistical analysis.** A one-way ANOVA with Dunnett’s post-hoc test or unpaired t-tests were performed (Graphpad Prism, version 6, USA), with p < 0.05 considered statistically significant. All averaged results are expressed as mean ± SEM values.

**References**

1. Scatton, B., Simon, H., Le Moal, M. & Bischoff, S. Origin of dopaminergic innervation of the rat hippocampal formation. *Neurosci Lett* **18**, 125–131 (1980).
2. Smith, Y. & Villalba, R. Striatal and extrastriatal dopamine in the basal ganglia: an overview of its anatomical organization in normal and Parkinsonian brains. * Mov Disord Suppl3, S34–S47 (2008).*
3. Bannon, M. J., Wolf, M. E. & Roth, R. H. Pharmacology of dopamine neurons innervating the prefrontal, cingulate and piriform cortices. * Eur J Pharmacol 92*, 119–125 (1983).
4. Tritsch, N. K. & Sabatini, B. L. Dopaminergic modulation of synaptic transmission in cortex and striatum. * Neuron 76*, 33–50 (2012).
5. Jokinen, P. et al. Impaired cognitive performance in Parkinson’s disease is related to caudate dopaminergic hypofunction and hippocampal atrophy. *Parkinsonism Relat Disor 15*, 88–93 (2009).
6. Bagot, R. C. et al. Ventral hippocampal afferents to the nucleus accumbens regulate susceptibility to depression. * Nat Commun 6*, 7062 (2015).
7. Fanselow, M. S. & Dong, H. W. Are the dorsal and ventral hippocampus functionally distinct structures? * Neuron 65*, 7–19 (2010).
8. Strange, B. A., Witter, M. P., Lein, E. S. & Moser, E. L. Functional organization of the hippocampal longitudinal axis. * Nat Rev Neurosci 15*, 655–669 (2014).
9. Engert, F. & Bonhoeffer, T. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. * Nature 399*, 66–70 (1999).
10. Guo, L. et al. Dynamic rewiring of neural circuits in the motor cortex in mouse models of Parkinson’s disease. * Nat Neurosci 18*, 1299–1309 (2015).
11. Kwon, H. B. & Sabatini, B. L. Glutamate induces de novo growth of functional spines in developing cortex. * Nature 474*, 100–104 (2011).
12. Hernandez, V. S. et al. Dopamine receptor dysregulation in hippocampus of aged rats underlies chronic pulsatile L-Dopa treatment induced cognitive and emotional alterations. * Neuropharmacology 82*, 88–100 (2014).
13. Lisman, J., Grace, A. A. & Duzel, E. A neoHebbian framework for episodic memory: role of dopamine-dependent late LTP. * Trends Neurosci 34*, 536–547 (2011).
14. Henry, C. et al. Morphological evidence for a dopaminergic terminal field in the hippocampal formation of young and adult rat. *Neuroscience 14*, 1039–1052 (1985).
15. Castner, S. A., Williams, G. V. & Goldman-Rakic, P. S. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. * Science 287*, 2020–2022 (2000).
16. Swati, J. & Wagner, J. I. Dopamine transporter blockade increases LTP in the CA1 region of the rat hippocampus via activation of the D3 dopamine receptor. * Learn Mem 13*, 161–167 (2006).
17. Calabresi, P., Castrioto, A., Di Filippo, M. & Picconi, B. New experimental and clinical links between the hippocampus and the dopaminergic system in Parkinson’s disease. * Lancet Neurol 12*, 811–821 (2013).
18. Rieu, I. et al. Impact of Mood and Behavioral Disorders on Quality of Life in Parkinson’s disease. * J Parkinsons Dis* (2016).
19. Gustafssohn, H., Nordstrom, A. & Nordstrom, P. Depression and subsequent risk of Parkinson disease: A nationwide cohort study. * Neurology 84*, 2422–2429 (2015).
20. Pain, S. et al. Toxicity of MPTP on neurotransmission in three mouse models of Parkinson’s disease. * Exp Toxicol Pathol 65*, 689–694 (2013).
21. Lee, K. W. et al. Neuroprotective and anti-inflammatory properties of a coffee component in the MPTP model of Parkinson’s disease. * Neurotherapeutics 10*, 143–153 (2013).
22. Zhu, G., Chen, Y., Huang, Y., Li, Q. & Behnisch, T. MPTP-mediated hippocampal dopamine deprivation modulates synaptic transmission and activity-dependent synaptic plasticity. * Toxicol Appl Pharmacol 254*, 332–341 (2011).
23. Zhu, G., Huang, Y., Chen, Y., Zhuang, Y. & Behnisch, T. MPTP modulates hippocampal synaptic transmission and activity-dependent synaptic plasticity via dopamine receptors. * J Neurochem 122*, 582–593 (2012).
24. Sulzer, D., Sanders, M. S., Poulsen, N. W. & Galli, A. Mechanisms of neurotransmitter release by amphetamines: a review. * Prog Neurobiol 75*, 406–433 (2005).
25. Kahlig, K. M. et al. Amphetamine induces dopamine efflux through a dopamine transporter channel. Proc Natl Acad Sci USA 102, 3495–3500 (2005).

26. Cools, R. & D'Esposito, M. Inverted-U-shaped dopamine actions on human working memory and cognitive control. Biol Psychiatry 69, e113–e125 (2011).

27. Jones, S. & Kauer, J. A. Amphetamine depresses excitatory synaptic transmission via serotonin receptors in the ventral tegmental area. J Neurosci 19, 9780–9787 (1999).

28. Nicola, S. M., Kombian, S. B. & Malenka, R. C. Psychostimulants depress excitatory synaptic transmission in the nucleus accumbens via presynaptic D1-like dopamine receptors. J Neurosci 16, 1591–1604 (1996).

29. Xia, Y. F., He, L., Whistler, J. L. & Hjelmdstad, G. O. Acute amphetamine exposure selectively desensitizes kappa-opioid receptors in the nucleus accumbens. Neuropsychopharmacology 33, 892–900 (2008).

30. Korber, C. & Kauer, T. Molecular Machines Regulating the Release Probability of Synaptic Vesicles at the Active Zone. Front Synaptic Neurosci 8, 5 (2016).

31. Piercey, M. F. Pharmacology of pramipexole, a dopamine D3-prefering agonist useful in treating Parkinson’s disease. Clin Neuropharmacol 21, 141–151 (1998).

32. Finkelstein, D. I. et al. Axonal sprouting following lesions of the rat substantia nigra. Neuroscience 97, 99–112 (2000).

33. Barone, P. et al. Pramipexole for the treatment of depressive symptoms in patients with Parkinson’s disease: a randomised, double-blind, placebo-controlled trial. Lancet Neurol 9, 573–580 (2010).

34. Schulte-Herbrüggen, O., Vogt, M. A., Hortnagl, H., Gass, P. & Hellweg, R. Pramipexole is active in depression tests and modulates monoaminergic transmission, but not brain levels of BDNF in mice. Eur J Pharmacol 677, 77–86 (2012).

35. Lee, J. et al. Sprouting of dopaminergic terminals and altered dopamine release and uptake in Parkinsonian dyskinesia. Brain 131, 1574–1587 (2008).

36. Stanic, D., Finkelstein, D. I., Bourke, D. W., Drago, J. & Horne, M. K. Timecourse of striatal re-innervation following lesions of dopaminergic SNpc neurons of the rat. J Neurosci 18, 1175–1188 (2003).

37. Kouvaros, S. & Papatheodoropoulos, C. Theta burst stimulation-induced LTP: Differences and similarities between the dorsal and ventral CA1 hippocampal synapses. Hippocampus 26, 1542–1559 (2016).

38. Borgquist, A. et al. Loss of Striatonigral GABAergic Presynaptic Inhibition Enables Motor Sensitization in Parkinsonian Mice. Neuron 87, 976–988 (2015).

39. Rosen, Z. B., Cheung, S. & Siegelbaum, S. A. Midbrain dopamine neurons bidirectionally regulate CA3-CA1 synaptic drive. Nat Neurosci 18, 1763–1771 (2015).

40. Bach, M. E. et al. Age-related defects in spatial memory are correlated with defects in the late phase of hippocampal long-term potentiation in vitro and are attenuated by drugs that enhance the cAMP signaling pathway. Proc Natl Acad Sci USA 96, 5280–5285 (1999).

41. Frey, U., Huang, Y. Y. & Kandel, E. R. Effects of cAMP simulates a late stage of LTP in hippocampal CA1 neurons. Science 260, 1661–1664 (1993).

42. Frey, U., Matthies, H., Reymann, K. G. & Matthies, H. The effect of dopaminergic D1 receptor blockade during tetanization on the expression of long-term potentiation in the rat CA1 region in vitro. Neurosci Lett 129, 111–114 (1991).

43. Huang, Y. Y. & Kandel, E. R. D1/D5 receptor agonists induce a protein synthesis-dependent late potentiation in the CA1 region of the hippocampus. Proc Natl Acad Sci USA 92, 2446–2450 (1995).

44. Muthane, U. et al. Differences in nigral neuron number and sensitivity to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine in C57/bl and CD-1 mice. Exp Neurol 126, 195–204 (1994).

45. Costa, C. et al. Mechanisms underlying the impairment of hippocampal long-term potentiation and memory in experimental Parkinson’s disease. Brain 135, 1884–1899 (2012).

46. Moriguchi, S., Yabuki, Y. & Fukunaga, K. Reduced calcium/calmodulin-dependent protein kinase II activity in the hippocampus is associated with impaired cognitive function in MPTP-treated mice. J Neurochem 120, 541–551 (2012).

47. Zhu, G., Li, J., He, L., Wang, X. & Hong, X. MPTP-induced changes in hippocampal synaptic plasticity and memory are prevented by memantine through the BDNF-TrkB pathway. Br J Pharmacol 172, 2354–2366 (2015).

48. Sherwood, J. L. et al. Differences in kainate receptor involvement in hippocampal mossy fibre long-term potentiation depending on slice orientation. Neurochem Int 61, 482–489 (2012).

49. Huemmeke, M., Eysel, U. T. & Mittmann, T. Lesion-induced enhancement of LTP in rat cortex is mediated by NMDA receptors containing the NR2B subunit. J Physiol 559, 875–882 (2004).

50. Logue, O. C., Cramer, N. P., Xu, X., Perl, D. P. & Galdzicki, Z. Alterations of functional properties of hippocampal networks following repetitive closed-head injury. Exp Neurol 277, 227–243 (2016).

51. Gramage, E., Del Olmo, N., Fole, A., Martin, Y. B. & Herradon, G. Periaxedolent amphetamine treatment causes transient cognitive disruptions and long-term changes in hippocampal LTP depending on the endogenous expression of pleiotropin. Addict Biol 18, 19–29 (2013).

52. Siciliano, C. A., Calipari, E. S. & Jones, S. R. Amphetamine potency varies with dopamine uptake rate across striatal subregions. J Neurosci 131, 348–355 (2014).

53. Huang, Y. C., Wang, S. J., Chiu, L. C. & Gean, P. W. Mediation of amphetamine-induced long-term depression of synaptic transmission by CB1 cannabinoid receptors in the rat amygdala. J Neurosci 23, 10311–10320 (2003).

54. Hammad, H. & Wagner, J. J. Dopamine-mediated disinhibition in the CA1 region of rat hippocampus via D3 receptor activation. J Pharmacol Exp Ther 316, 113–120 (2006).

55. Börggärd-Maciejewska, K. et al. Pramipexole but not imipramine or fluoxetine reverses the “depressive-like” behaviour in a rat model of preclinical stages of Parkinson’s disease. Behav Brain Res 271, 343–354 (2014).

56. Joyce, J. N. & Millan, M. J. Dopamine D3 receptor agonists for protection and repair in Parkinson’s disease. Curr Opin Pharmacol 7, 100–105 (2007).

57. Carvey, P. M., McGuire, S. O. & Ling, Z. D. Neuroprotective effects of D3 dopamine receptor agonists. Parkinsonism Relat Disord 7, 213–223 (2001).

58. Lei, P. et al. Tau deficiency induces parkinsonism with dementia by impairing APP-mediated iron export. Nat Med 18, 291–295 (2012).

59. Parish, C. L. et al. Haloperidol treatment reverses behavioural and anatomical changes in cocaine-dependent mice. Neurobiol Dis 19, 301–311 (2005).

60. Reyes, A. Influence of dendritic conductances on the input-output properties of neurons. Annu Rev Neurosci 24, 653–675 (2001).

61. Branco, T. & Barra, K. The probability of neurotransmitter release: variability and feedback control at single synapses. Nat Rev Neurosci 10, 373–383 (2009).

62. Sesack, S. R., Carr, D. B., Omelchenko, N. & Pinto, A. Anatomical substrates for glutamate-dopamine interactions: evidence for specificity of connections and extrasynaptic actions. Ann N Y Acad Sci 1003, 36–52 (2003).

63. Hyman, S. E. & Malenka, R. C. Addiction and the brain: the neurobiology of compulsion and its persistence. Nat Rev Neurosci 2, 695–703 (2001).
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Author Contributions
J.C.-H. and D.F. designed experiments; J.C.-H. performed research; J.C.-H. and D.F. analyzed data; J. C.-H., P.A. and D.F. wrote the paper.

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