



Article Amitriptyline Accelerates SERT Binding Recovery in a Rat 3,4-Methylenedioxymethamphetamine (MDMA) Model: In Vivo 4-[¹⁸F]-ADAM PET Imaging

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Abstract: Numerous studies have confirmed that 3,4-Methylenedioxymethamphetamine (MDMA) produces long-lasting changes to the density of the serotonin reuptake transporter (SERT). Amitriptyline (AMI) has been shown to exert neuroprotective properties in neuropathologic injury. Here, we used a SERT-specific radionuclide, 4-[¹⁸F]-ADAM, to assess the longitudinal alterations in SERT binding and evaluate the synergistic neuroprotective effect of AMI in a rat MDMA model. In response to MDMA treatment regimens, SERT binding was significantly reduced in rat brains. Region-specific recovery rate (normalized to baseline) in the MDMA group at day 14 was 71.29% \pm 3.21%, and progressively increased to 90.90% \pm 7.63% at day 35. AMI dramatically increased SERT binding in all brain regions, enhancing average ~18% recovery rate at day 14 when compared with the MDMA group. The immunochemical staining revealed that AMI markedly increased the serotonergic fiber density in the cingulate and thalamus after MDMA-induction, and confirmed the PET findings. Using in vivo longitudinal PET imaging, we demonstrated that SERT recovery was positively correlated with the duration of MDMA abstinence, implying that lower SERT densities in MDMA-induced rats reflected neurotoxic effects and were (varied) region-specific and reversible. AMI globally accelerated the recovery rate of SERT binding and increased SERT fiber density with possible neuroprotective effects.

Keywords: 4-[¹⁸F]-ADAM; MDMA; SERT; amitriptyline

1. Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is a ring-substituted derivative of amphetamine that induces hallucinogenic effects [1]. MDMA has been demonstrated to reduce serotonin levels, serotonin reuptake transporter (SERT), and the amount of serotonin synthesis tryptophan hydroxylase important to enzymes after the use of MDMA has significantly reduced [2–5]. These phenomena occur because of the effects of MDMA on serotonin neurons injury and MDMA inhibition of the presynaptic neuron into the tryptophan hydroxylase enzyme and the disintegration of monoamine oxidase-B (MAO-B).



Citation: Tsai, C.-J.; Chiu, C.-H.; Kuo, Y.-Y.; Huang, W.-S.; Yu, T.-H.; Flores, L.G., II; Yeh, S.H.-H.; Ma, K.-H. Amitriptyline Accelerates SERT Binding Recovery in a Rat 3,4-Methylenedioxymethamphetamine (MDMA) Model: In Vivo 4-[¹⁸F]-ADAM PET Imaging. *Int. J. Mol. Sci.* **2022**, *23*, 7035. https:// doi.org/10.3390/ijms23137035

Academic Editors: Matteo Marti, Liana Fattore, Carlo Locatelli and Monia Lenzi

Received: 1 June 2022 Accepted: 22 June 2022 Published: 24 June 2022

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Copyright: © 2022 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https:// creativecommons.org/licenses/by/ 4.0/). Serotonin concentrations rose sharply after MDMA administration but quickly dropped in a few moments [6,7].

SERT is one of the pharmacological and toxic biological targets of MDMA. The SERT involvement in the MDMA-induced neurotoxicity mechanism has been extensively studied [8–10]. The neuroprotective effect of selective serotonin reuptake inhibitors (SSRIs) (i.e., fluoxetine) has been studied in a rat model after MDMA intoxication [11,12]. In addition, co-administration of MDMA with SSRIs (e.g., fluoxetine and citalopram) can prevent subsequent extracellular oxidative stress [13], long-term serotonin depletion and serotonin uptake site decrease, indicating that free radical production might occur following SERT activation by MDMA [14–16].

Amitriptyline (AMI) is one of the earliest members of the tricyclic anti-depressant family. AMI functions as a SERT inhibitor (ki = 1 nM), norepinephrine transport reuptake (NET) inhibitor (ki = 35 nM), and dopamine transport reuptake (DAT) inhibitor (ki = 3780 nM) [17,18]. AMI is also effective for the therapy of some mental disorders and the treatment of neuropathic pain [19,20]. AMI seems to be more highly effective than newer SSRIs [21,22]. Regarding anti-depressant actions, AMI induces dose-dependent pluripotent actions of this drug [18,23]. Interestingly, several studies confirm that AMI elicits strong neurotrophic activity via a productive interaction with the brain-derived neurotrophic factor (BDNF) and the neurotrophic tyrosine kinase receptor B (TrkB) system [19,24–26]. Kamińska et al. (2018) reported that chronic treatment with AMI in a unilaterally 6-hydroxydopamine lesion rat model increased dopamine levels. However, it decreased SERT and NET levels in the striatum and substantia nigra as well as improved motor dysfunction [27]. However, the in vivo interaction neurotoxicity remains unknown.

Nuclear medicine has emerged as a vital imaging technique for detection of molecular serotonin transporter distribution in the central nervous system. Indeed, there are a number of SERT imaging agents available for human PET imaging studies. Some of these agents labeled with 11C or 18F have been used for MDMA-related neuroimaging, including [¹¹C]-(+) McN5652 [28,29], [¹¹C]DASB [30–32], [¹¹C]AFM [33], [¹¹C]MDL 100907 [31], S-[¹⁸F]fluoroethyl)-(+)-McN5652 [34], S-[¹⁸F]fluoromethyl)-(+)-McN5652 [35], and [¹⁸F]F-ACF [36].

Throughout the last ten years, we developed the 18F-labeled SERT radioligand, N,N-dimethyl-2-(2-amino-4-[¹⁸F]-fluorophenylthio) benzylamine (4-[¹⁸F]-ADAM) selective PET imaging agent for SERT, 4-[¹⁸F]-ADAM, and demonstrated its selectivity, specificity, and safety for use in rodent or primate models [37–41] and human study [42]. Furthermore, we demonstrated that the SSRI fluoxetine produced long-lasting protection against MDMA-induced neurotoxicity [10] and the MDMA-induced decrease in brain SERT levels, which could persist for over four years in primates [4].

In light of these findings, this study aimed to use PET 4-[¹⁸F]-ADAM to assess (1) the long-term and regional-specific neuronal damage or recovery of SERT after MDMA administration with advanced 3D PET/MR imaging, and (2) the evaluation of AMI against MDMA neurotoxicity in rat brain.

2. Results

2.1. SERT Recovery Is Region-Specific and Time-Dependent

Figure 1 shows example images of the location of the brain regions used to estimate SERT binding using 4-[¹⁸F]-ADAM. The 3D 4-[¹⁸F]-ADAM PET images in the rat brain are shown in Figure 2. Brain uptake of 4-[¹⁸F]-ADAM in all regions was significantly lower in rats pretreated with MDMA than in control rats from day 14 to day 35 (second row).

However, the uptake in the control groups was similar in each imaging data set (top row). In the baseline, the hypothalamus showed the highest 4-[¹⁸F]-ADAM uptake, followed by the midbrain, thalamus, striatum, hippocampus posterior, motor cortex, cingulate cortex, anterodorsal hippocampus, auditory cortex, and visual cortex (Figure 3 black line).



Figure 1. 3D 4-[¹⁸F]-ADAM PET images Illustration of 9 brain areas of interest (ROIs) used to estimate SERT binding of 4-[¹⁸F]-ADAM.



Figure 2. Cont.



Figure 2. 3D quantitative 4-[¹⁸F]-ADAM PET images in different brain areas. 4-[¹⁸F]-ADAM binding to SERT in the motor cortex, cingulate cortex, auditory cortex, visual cortex, and thalamus, striatum, hippocampus, and anterodorsal hippocampus. In general, the uptake of 4-[¹⁸F]-ADAM in all 9 regions was significantly reduced in MDMA group as compared to the controls and was gradually increased from day 14 to day 35 (second row). MDMA with AMI pretreatment demonstrated progressive and significant increase in the uptake of 4-[¹⁸F]-ADAM (third row) whereas AMI alone had no effect on the uptake of 4-[¹⁸F]-ADAM (fourth row).



Figure 3. Specific uptake ratios (SURs) of 4-[¹⁸F]-ADAM of baseline and on day 7, 14, 21, 28 and 35 from the beginning of the 4-day treatment in rat brain regions. Compared to the control (black lines), MDMA administration resulted in significant reduction the SURs of 4-[¹⁸F]-ADAM from day 14 to day 28 and returned to the baseline on day 35 (red line, red * p < 0.05, ** p < 0.01, *** p < 0.005, Group B-MDMA vs. Group A-control). MDMA with AMI pretreatment showed remarkable increase of 4-[¹⁸F]-ADAM binding as compared to the MDMA group (blue line, blue # p < 0.05, ## p < 0.01, Group C-MDMA+AMI vs. Group B- MDMA). AMI alone (green lines) showed a similar pattern of SURs to that in the control (black lines) throughout the study. Data are mean ± SD. Detailed statistical results between each group are summarized in Figure 4.

Group	Striatum	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA
А	Control	1.97 ± 0.23	1.89 ± 0.07				2.02 ± 0.23				1.98 ± 0.29				2.10 ± 0.44			
в	MDMA	2.23 ± 0.48	1.63 ± 0.19	•			1.65 ± 0.29	ns			1.89 ± 0.01	ns			2.16 ± 0.07	ns		
С	AMI+MDMA	1.96 ± 0.04	1.72 ± 0.10	ns	##		1.79 ± 0.17	ns	#		1.88 ± 0.24	ns	ns		2.08 ± 0.17	ns	ns	
D	AMI	2.17 ± 0.27	2.14 ± 0.26	ns	###	ns	2.23 ± 0.40	ns	#	ns	2.02 ± 0.28	ns	#	ns	2.37 ± 0.39	ns	ns	ns
Group	uditoryCorte	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA
A	Control	1.47 ± 0.13	1.55 ± 0.06				1.65 ± 0.29				1.89 ± 0.01				2.16 ± 0.07			
в	MDMA	1.59 ± 0.17	1.18 ± 0.07	***			1.36 ± 0.21	ns			1.25 ± 0.05				1.46 ± 0.24	ns		
С	AMI+MDMA	1.61 ± 0.04	1.36 ± 0.15		#		1.39 ± 0.17	ns	ns		1.30 ± 0.12		ns		1.57 ± 0.28	ns	ns	
D	AMI	1.64 ± 0.17	1.53 ± 0.20	ns	####	а	1.65 ± 0.21	ns	#	а	1.47 ± 0.18	ns	#	а	1.70 ± 0.24	ns	ns	ns
Group	ingulateCorte	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA
А	Control	1.71 ± 0.14	1.59 ± 0.13				1.86 ± 0.24				1.76 ± 0.24				1.94 ± 0.45			
В	MDMA	1.92 ± 0.42	1.26 ± 0.15	•			1.34 ± 0.19				1.38 ± 0.04				1.72 ± 0.14	ns		
С	AMI+MDMA	1.79 ± 0.28	1.66 ± 0.29	ns	#		1.58 ± 0.23		ns		1.45 ± 0.13		#		1.68 ± 0.30	ns	ns	
D	AMI	1.90 ± 0.10	1.89 ± 0.22	•	####	а	1.93 ± 0.32	ns	##	а	1.76 ± 0.21	ns	##	аа	2.00 ± 0.13	*	#	а
-																		
Group	MotorCortex	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA
А	Control	1.81 ± 0.15	1.77 ± 0.06				1.91 ± 0.12				1.87 ± 0.16				1.97 ± 0.31			
В	MDMA	1.99 ± 0.33	1.47 ± 0.21				1.61 ± 0.18	ns			1.59 ± 0.11	ns			1.91 ± 0.12	ns		
С	AMI+MDMA	2.04 ± 0.16	1.77 ± 0.22	ns	##		1.78 ± 0.14	ns	ns		1.71 ± 0.12	ns	ns		1.87 ± 0.30	ns	ns	
D	AMI	1.94 ± 0.11	1.90 ± 0.15	ns	####	*	2.02 ± 0.29	ns	#	а	1.89 ± 0.14	ns	##	а	2.11 ± 0.27	ns	ms	ns
Group	VisualCortex	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA
А	Control	1.35 ± 0.15	1.37 ± 0.07				1.38 ± 0.03				1.38 ± 0.15				1.50 ± 0.26			
В	MDMA	1.41 ± 0.15	1.17 ± 0.08	•			1.21 ± 0.18	ns			1.25 ± 0.14	ns			1.41 ± 0.19	ns		
С	AMI+MDMA	1.41 ± 0.12	1.30 ± 0.16	ns	ns		1.30 ± 0.16	ns	ns		1.33 ± 0.12	ns	ns		1.52 ± 0.19	ns	ns	
D	AMI	1.43 ± 0.15	1.46 ± 0.13	ns	####	а	1.50 ± 0.12	ns	#	а	1.46 ± 0.14	ns	#	ns	1.66 ± 0.12	ns	ns	ns
Group	ampusAnterc	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA
Group A	ampusAnterc Control	Baseline 1.56 ± 0.12	14 days 1.64 ± 0.03	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days 1.61 ± 0.20	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days 1.38 ± 0.15	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days 1.50 ± 0.26	Pvs Control	Pvs MDMA	Pvs AMI+MDMA
Group A B	ampusAnterc Control MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.31	14 days 1.64 ± 0.03 1.21 ± 0.18	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days 1.61 ± 0.20 1.24 ± 0.28	Pvs Control ns	Pvs MDMA	Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.10	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days 1.50 ± 0.26 1.63 ± 0.11	Pvs Control ns	Pvs MDMA	Pvs AMI+MDMA
Group A B C	ampusAnterc Control MDMA AMI+MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25	Pvs Control	Pvs MDMA #	Pvs AMI+MDMA 	21 days 1.61 ± 0.20 1.24 ± 0.28 1.20 ± 0.62	Pvs Control ns ns	Pvs MDMA ns	Pvs AMI+MDMA 	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15	Pvs Control	Pvs MDMA #	Pvs AMI+MDMA	35 days 1.50 ± 0.26 1.63 ± 0.11 1.71 ± 0.30	Pvs Control ns ns	Pvs MDMA ns	Pvs AMI+MDMA
Group A B C D	ampusAnterc Control MDMA AMI+MDMA AMI	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25 1.76 ± 0.24	Pvs Control ns ns	Pvs MDMA # ####	Pvs AMI+MDMA a	21 days 1.61 ± 0.20 1.24 ± 0.28 1.20 ± 0.62 1.76 ± 0.29	Pvs Control ns ns ns	Pvs MDMA ns #	Pvs AMI+MDMA ns	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.18	Pvs Control	Pvs MDMA # ##	Pvs AMI+MDMA ns	35 days 1.50 ± 0.26 1.63 ± 0.11 1.71 ± 0.30 1.86 ± 0.31	Pvs Control ns ns ns	Pvs MDMA ns ns	Pvs AMI+MDMA ns
Group A B C D	ampusAnterc Control MDMA AMI+MDMA AMI	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25 1.76 ± 0.24	Pvs Control	Pvs MDMA # ####	Pvs AMI+MDMA a	21 days 1.61 ± 0.20 1.24 ± 0.28 1.20 ± 0.62 1.76 ± 0.29	Pvs Control ns ns ns	Pvs MDMA ns #	Pvs AMI+MDMA ns	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.18	Pvs Control	Pvs MDMA # ##	Pvs AMI+MDMA	35 days 1.50 ± 0.26 1.63 ± 0.11 1.71 ± 0.30 1.86 ± 0.31	Pvs Control ns ns ns	Pvs MDMA ns ns	Pvs AMI+MDMA ns
Group A B C D Group	ampusAnterc Control MDMA AMI+MDMA AMI ocampusPost	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25 1.76 ± 0.24 14 days	Pvs Control	Pvs MDMA # ### Pvs MDMA	Pvs AMI+MDMA a Pvs AMI+MDMA	21 days 1.61 ± 0.20 1.24 ± 0.28 1.20 ± 0.62 1.76 ± 0.29	Pvs Control ns ns ns Pvs Control	Pvs MDMA ns # Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.18	Pvs Control	Pvs MDMA # ##	ns	35 days 1.50 ± 0.26 1.63 ± 0.11 1.71 ± 0.30 1.86 ± 0.31 35 days	Pvs Control	Pvs MDMA ns ns Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA
Group A C D Group A	ampusAnterc Control MDMA AMI+MDMA AMI ocampusPost Control	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25 1.76 ± 0.24 14 days 1.84 ± 0.11	Pvs Control ++ NS NS Pvs Control	Pvs MDMA # ### Pvs MDMA 	Pvs AMI+MDMA a Pvs AMI+MDMA	21 days 1.61 ± 0.20 1.24 ± 0.28 1.20 ± 0.62 1.76 ± 0.29	Pvs Control ns ns ns ns Pvs Control	Pvs MDMA ns # Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA 	28 Jays 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.18 28 days 1.99 ± 0.09	Pvs Control	Pvs MDMA # ## vs AMI+MDN 	ns M. Pvs AMI+MDMA	35 days 1.50 ± 0.26 1.63 ± 0.11 1.71 ± 0.30 1.86 ± 0.31 35 days 2.02 ± 0.29	Pvs Control ns ns Pvs Control 	Pvs MDMA ns ns Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA
Group A C D Group A B	ampusAnterc Control MDMA AMI+MDMA AMI ocampusPost Control MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25 1.76 ± 0.24 14 days 1.84 ± 0.11 1.48 ± 0.26	Pvs Control ** ns ns Pvs Control	Pvs MDMA # ### Pvs MDMA 	Pvs AMI+MDMA a Pvs AMI+MDMA 	21 days 1.61 ± 0.20 1.24 ± 0.28 1.20 ± 0.62 1.76 ± 0.29 21 days 2.06 ± 0.31 1.45 ± 0.31	Pvs Control ns ns ns Pvs Control ••	Pvs MDMA ns # Pvs MDMA 	Pvs AMI+MDMA ns Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.18 28 days 1.99 1.50 ± 0.09 1.50 ± 0.13	Pvs Control ++ + ns Pvs Control	Pvs MDMA # ## vs AMI+MDM 	ns M, Pvs AMI+MDMA N, Pvs AMI+MDMA	35 days 1.50 ± 0.26 1.63 ± 0.11 1.71 ± 0.30 1.86 ± 0.31 35 days 2.02 ± 0.29 1.91 ± 0.16	Pvs Control ns ns ns ns	Pvs MDMA ns ns Pvs MDMA	Pvs AMI+MDMA
Group A C D Group A B C	ampusAnterc Control MDMA AMI+MDMA AMI ocampusPost Control MDMA AMI+MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25 1.76 ± 0.24 14 days 1.84 ± 0.11 1.48 ± 0.26 1.81 ± 0.29	Pvs Control	Pvs MDMA # # ### Pvs MDMA #	Pvs AMI+MDMA a Pvs AMI+MDMA 	$\begin{array}{c c} \textbf{21 days} \\ \hline 1.61 & \pm & 0.20 \\ 1.24 & \pm & 0.28 \\ 1.20 & \pm & 0.62 \\ \hline 1.76 & \pm & 0.29 \\ \hline \textbf{21 days} \\ \hline \textbf{2.06} & \pm & 0.31 \\ 1.45 & \pm & 0.31 \\ 1.48 & \pm & 0.23 \\ \end{array}$	Pvs Control ns ns ns Pvs Control ns	Pvs MDMA ns # Pvs MDMA #	Pvs AMI+MDMA ns Pvs AMI+MDMA 	28 dəys 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.18 28 dəys 1.99 ± 0.09 1.50 ± 0.13 1.61 ± 0.19	Pvs Control •• • ns Pvs Control •• ••	<u>Pvs MDMA</u> # ## vs AMI+MDN #	Pvs AMI+MDMA ns M. Pvs AMI+MDMA 	35 days 1.50 ± 0.26 1.63 ± 0.11 1.71 ± 0.30 1.86 ± 0.31 35 days 2.02 ± 0.29 1.91 ± 0.16 1.94 ± 0.33	Pvs Control ns ns ns Pvs Control ns ns ns	Pvs MDMA ns ns	Pvs AMI+MDMA ns Pvs AMI+MDMA
Group A C D Group A B C D	ampusAnterc Control MDMA AMI+MDMA AMI ocampusPost Control MDMA AMI+MDMA AMI	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25 1.76 ± 0.24 14 days 1.84 ± 0.11 1.84 ± 0.26 1.81 ± 0.29 2.12 ± 0.21	Pvs Control	Pvs MDMA # #### Pvs MDMA # # ####	Pvs AMI+MDMA a Pvs AMI+MDMA aa	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Pvs Control ns ns ns Pvs Control ns ns ns	Pvs MDMA ns # Pvs MDMA # #	Pvs AMI+MDMA ns Pvs AMI+MDMA ns	28 ख्रेप् 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.18 2 1.90 ± 0.09 1.50 ± 0.13 1.61 ± 0.19 1.90 ± 0.24	Pvs Control Pvs Control 	Pvs MDMA # ## vs AMI+MDN # ###	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a	35 Jay 1.50 ± 0.26 1.63 ± 0.31 1.71 ± 0.30 35 Jay ± 0.31 2.02 ± 0.20 1.94 ± 0.33 2.22 ± 0.11	Pvs Control ns ns ns ns Pvs Control ns ns ns *	Pvs MDMA ns ns ns ns + ns ++	Pvs AMI+MDMA ns Pvs AMI+MDMA ns
Group A B C D Group A B C D	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA AMI	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25 1.76 ± 0.24 14 days 1.84 ± 0.11 1.48 ± 0.26 1.81 ± 0.29 2.12 ± 0.21	Pvs Control	Pvs MDMA # #### Pvs MDMA # ####	Pvs AMI+MDMA a Pvs AMI+MDMA aa	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Pvs Control	Pvs MDMA ns # Pvs MDMA # # #	Pvs AMI+MDMA ns Pvs AMI+MDMA ns	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.18 Value 1.99 ± 0.09 1.50 ± 0.13 1.61 ± 0.13 1.61 ± 0.12 1.99 1.90 1.90 1.90	Pvs Control	Pvs MDMA # ## vs AMI+MDN # ##	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a	35 days 1.50 ± 0.26 1.63 ± 0.31 1.71 ± 0.30 1.86 ± 0.31 35 days 2.02 ± 0.29 1.91 ± 0.33 2.22 ± 0.33 2.22 ± 0.33	Pvs Control ns ns ns Pvs Control ns s *	Pvs MDMA ns Pvs MDMA ns #	Pvs AMI+MDMA ns Pvs AMI+MDMA ns ns
Group A B C D Group A B C D Group	ampusAnterc Control MDMA AMI+MDMA AMI cocampusPost Control MDMA AMI+MDMA AMI 4ypothalamu:	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35 Baseline	14 days 1.64 ± 0.03 1.21 ± 0.18 1.51 ± 0.25 1.76 ± 0.24 14 days 1.84 ± 0.11 1.48 ± 0.26 1.81 ± 0.29 2.12 ± 0.21 14 days	Pvs Control	Pvs MDMA # #### Pvs MDMA # ### Pvs MDMA	Pvs AMIHMDMA a Pvs AMIHMDMA aa Pvs AMIHMDMA	$\begin{array}{c c} \textbf{21 days} \\ \textbf{1.61} & \pm & 0.20 \\ \textbf{1.24} & \pm & 0.28 \\ \textbf{1.20} & \pm & 0.62 \\ \textbf{1.76} & \pm & 0.29 \\ \hline \textbf{21 days} \\ \textbf{2.06} & \pm & 0.31 \\ \textbf{1.48} & \pm & 0.33 \\ \textbf{2.06} & \pm & 0.27 \\ \hline \textbf{21 days} \\ \textbf{2.16} & \textbf{2.16} \\ \textbf{2.16}$	Pvs Control nS nS Pvs Control nS nS Pvs Control Pvs Control	Pvs MDMA ns # Pvs MDMA # # Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.10 1.32 ± 0.15 1.62 ± 0.15 1.62 ± 0.16 1.62 ± 0.10 1.50 ± 0.10 1.50 ± 0.13 1.61 ± 0.19 1.99 ± 0.24	Pvs Control	Pvs MDMA # ## vs AMI+MDN # ## Pvs MDMA	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a Pvs AMI+MDMA	35 days 1.50 ± 0.26 1.63 ± 0.11 1.71 ± 0.30 1.86 ± 0.31 35 days 2.02 ± 0.29 9.91 ± 0.33 2.22 ± 0.11 35 days 35 days	Pvs Control ns ns ns ns ns Pvs Control ns Pvs Control ns ns	Pvs MDMA ns ns # Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA
Group A B C D Group A B C D Group A	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA AMI 1ypothalamu: Control	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35 Baseline 2.39 ± 0.43	$\begin{array}{r} \textbf{14 days} \\ \textbf{1.64 } \pm 0.03 \\ \textbf{1.21 } \pm 0.18 \\ \textbf{1.51 } \pm 0.25 \\ \textbf{1.76 } \pm 0.24 \\ \hline \textbf{14 days} \\ \textbf{1.84 } \pm 0.11 \\ \textbf{1.84 } \pm 0.26 \\ \textbf{1.81 } \pm 0.29 \\ \textbf{2.12 } \pm 0.21 \\ \hline \textbf{14 days} \\ \textbf{2.15 } \pm 0.18 \\ \textbf{2.15 } \pm 0.18 \\ \hline \textbf{2.15 } \pm 0.1$	Pvs Control	Pvs MDMA # # ### Pvs MDMA # # #### Pvs MDMA	Pvs AMI+MDMA B Pvs AMI+MDMA Pvs AMI+MDMA 	$\begin{array}{rrrr} \textbf{21 days} \\ 1.61 & \pm 0.20 \\ 1.24 & \pm 0.28 \\ 1.20 & \pm 0.62 \\ 1.76 & \pm 0.29 \\ \hline \textbf{21 days} \\ 2.06 & \pm 0.31 \\ 1.45 & \pm 0.31 \\ 2.06 & \pm 0.23 \\ 2.06 & \pm 0.27 \\ \hline \textbf{21 days} \\ 2.52 & \pm 0.43 \\ \hline \textbf{2.52 & \pm 0.43} \\ \hline$	Pvs Control	Pvs MDMA ns # Pvs MDMA # # Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.15 1.33 ± 0.15 1.62 ± 0.15 1.62 ± 0.15 1.62 ± 0.15 1.62 ± 0.15 1.62 ± 0.19 1.99 ± 0.09 1.50 ± 0.11 1.61 ± 0.12 1.90 ± 0.24 28 days ± 0.24	Pvs Control	Pvs MDMA # # ## vs AMI+MDN # # ## Pvs MDMA	Pvs AMI+MDMA ns M, Pvs AMI+MDMA 	$\begin{array}{rrrr} \textbf{35 days} \\ 1.50 & \pm 0.26 \\ 1.63 & \pm 0.11 \\ 1.71 & \pm 0.30 \\ 1.86 & \pm 0.31 \\ \hline \textbf{35 days} \\ 2.02 & \pm 0.29 \\ 1.91 & \pm 0.16 \\ 1.94 & \pm 0.33 \\ 2.22 & \pm 0.11 \\ \hline \textbf{35 days} \\ 2.29 & \pm 0.15 \\ \hline \textbf{35 days} \\ 2.29 & \pm 0.15 \\ \hline \textbf{35 days} \\ \hline \textbf$	Pvs Control ns ns ns ns 	Pvs MDMA ns ns Pvs MDMA ns # Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA TT
Group A B C D Group A B C C D C C D C A B C C D C C C C C C C C C C C C C C C C	ampusAnterc Control MDMA AMI+MDMA AMI ocampusPost Control MDMA AMI+MDMA AMI typothalamu: Control MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.32 Baseline 2.39 ± 0.43 2.39 ± 0.43	$\begin{array}{c} \textbf{14 days} \\ \textbf{1.64 } \pm 0.03 \\ \textbf{1.21 } \pm 0.03 \\ \textbf{1.51 } \pm 0.25 \\ \textbf{1.76 } \pm 0.24 \\ \hline \textbf{14 days} \\ \textbf{1.84 } \pm 0.11 \\ \textbf{1.48 } \pm 0.26 \\ \textbf{1.81 } \pm 0.29 \\ \textbf{2.12 } \pm 0.21 \\ \hline \textbf{14 days} \\ \textbf{2.15 } \pm 0.21 \\ \hline \textbf{14 days} \\ \textbf{14 } \textbf{2.15 } \textbf{1.51 } 1$	Pvs Control	Pvs MDMA # #### Pvs MDMA # ### Pvs MDMA	Pvs AMI+MDMA	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Pus Control	Pvs MDMA ns # Pvs MDMA # # 	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.18 28 days 1.59 ± 0.01 1.50 ± 0.13 1.61 ± 0.13 1.62 ± 0.13 1.64 ± 0.19 1.99 ± 0.24 2.81 ± 0.06 2.31 ± 0.25	Pvs Control	Pvs MDMA # # ## /s AMI+MDN # # ## Pvs MDMA	Pvs AMI+MDMA ns M, Pvs AMI+MDMA a Pvs AMI+MDMA 	$\begin{array}{cccc} \textbf{35 days} \\ 1.50 & \pm 0.26 \\ 1.63 & \pm 0.11 \\ 1.71 & \pm 0.30 \\ 1.86 & \pm 0.31 \\ \hline \textbf{35 days} \\ 2.02 & \pm 0.29 \\ 1.91 & \pm 0.16 \\ 1.94 & \pm 0.33 \\ 2.22 & \pm 0.11 \\ \hline \textbf{35 days} \\ 2.29 & \pm 0.15 \\ 2.43 & \pm 0.07 \\ \hline \textbf{2.43} & \pm 0.07 \\ \hline \textbf{3.5 days} \\ \hline $	Pvs Control nS nS nS nS Pvs Control nS nS nS nS	Pvs MDMA ns ns ms # Pvs MDMA 	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA
Group A B C D Group A B C D Group A B C C	ampusAnterc Control MDMA AMI+MDMA AMI Control MDMA AMI+MDMA AMI Control MDMA AMI+MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35 Baseline 2.39 ± 0.43 2.91 ± 0.52 2.66 ± 0.25	$\begin{array}{c} \textbf{14 days} \\ \textbf{1.64 } \pm \textbf{0.03} \\ \textbf{1.21 } \pm \textbf{0.18} \\ \textbf{1.51 } \pm \textbf{0.25} \\ \textbf{1.51 } \pm \textbf{0.25} \\ \textbf{1.76 } \pm \textbf{0.24} \\ \hline \\ \textbf{14 days} \\ \textbf{1.84 } \pm \textbf{0.11} \\ \textbf{1.84 } \pm \textbf{0.12} \\ \textbf{1.81 } \pm \textbf{0.29} \\ \textbf{2.12 } \pm \textbf{0.21} \\ \hline \\ \textbf{14 days} \\ \textbf{2.15 } \pm \textbf{0.18} \\ \textbf{1.92 } \pm \textbf{0.10} \\ \textbf{2.38 } \pm \textbf{0.42} \end{array}$	Pvs Control	Pvs MDMA 	Pvs AMI+MDMA	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Pvs Control ns ns Pvs Control The second se	Pvs MDMA 	Pvs AMI+MDMA ns Pvs AMI+MDMA Ns Pvs AMI+MDMA	28 Jays 1.38 ± 0.15 1.32 ± 0.15 1.34 ± 0.15 1.62 ± 0.18 28 Jays 1.99 ± 0.09 1.50 ± 0.13 1.61 ± 0.13 1.61 ± 0.19 1.90 ± 0.24 28 Jays ± 0.25	Pvs Control	Pvs MDMA ## ## ## ## Pvs MDMA ns	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a Pvs AMI+MDMA 	$\begin{array}{cccc} \textbf{35 days} \\ 1.50 & \pm 0.26 \\ 1.63 & \pm 0.11 \\ 1.71 & \pm 0.30 \\ 1.86 & \pm 0.31 \\ \hline \textbf{35 days} \\ 2.02 & \pm 0.29 \\ 1.91 & \pm 0.13 \\ 1.94 & \pm 0.33 \\ 2.22 & \pm 0.11 \\ \hline \textbf{35 days} \\ \textbf{2.29} & \pm 0.15 \\ \hline \textbf{2.29} & \pm 0.07 \\ 2.44 & \pm 0.07 \\ 2.44 & \pm 0.37 \\ \hline \textbf{2.44} & \pm 0.37 \\ \hline \textbf{2.45} & \pm 0.37 \\ \hline 2.45$	Pvs Control	Pvs MDMA ns ns ns # Pvs MDMA ns	Pvs AMI+MDMA ns Pvs AMI+MDMA Pvs AMI+MDMA
Group A B C D Group A B C C D Group C D D	ampusAnterc Control MDMA AMI+MDMA AMI+ Control MDMA AMI+MDMA AMI+ Control MDMA AMI+MDMA AMI+MDMA AMI+	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.36 ± 0.13 1.36 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35 Baseline 2.39 ± 0.43 2.39 ± 0.42 2.66 ± 0.25 2.69 ± 0.45	$\begin{array}{c} \textbf{14 days} \\ \textbf{1.64 } \pm 0.03 \\ \textbf{1.21 } \pm 0.18 \\ \textbf{1.51 } \pm 0.25 \\ \textbf{1.76 } \pm 0.24 \\ \hline \textbf{14 days} \\ \textbf{1.84 } \pm 0.11 \\ \textbf{1.48 } \pm 0.26 \\ \textbf{1.81 } \pm 0.29 \\ \textbf{2.12 } \pm 0.21 \\ \textbf{2.15 } \pm 0.18 \\ \textbf{1.92 } \pm 0.20 \\ \textbf{2.15 } \pm 0.18 \\ \textbf{1.92 } \pm 0.01 \\ \textbf{2.15 } \pm 0.18 \\ \textbf{1.92 } \pm 0.01 \\ \textbf{2.85 } \pm 0.42 \\ \textbf{2.65 } \pm 0.28 \\ \end{array}$	Pvs Control	Pvs MDMA # # #### Pvs MDMA Pvs MDMA ns ####	Pvs AMI+MDMA a a Pvs AMI+MDMA a Pvs AMI+MDMA a a a a a a a a a a a a a a a a a a a	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Pus Control	Pvs MDMA	Pvs AMI+MDMA Rvs AMI+MDMA ns Pvs AMI+MDMA ns ns ns ns	28 days 1.38 ± 0.15 1.32 ± 0.10 1.33 ± 0.15 1.62 ± 0.18 28 days 1.99 ± 0.01 1.50 ± 0.19 1.61 ± 0.19 1.94 ± 0.26 2.31 ± 0.02 2.31 ± 0.25 2.08 ± 0.23 2.08 ± 0.23 2.35 ± 0.37	Pvs Control	Pvs MDMA 	Nys AMI+MDMA ns M. Pvs AMI+MDMA a Pvs AMI+MDMA ns	$\begin{array}{cccc} \textbf{35 days} \\ 1.50 & \pm 0.26 \\ 1.63 & \pm 0.11 \\ 1.71 & \pm 0.30 \\ 1.86 & \pm 0.31 \\ \hline \textbf{35 days} \\ 2.02 & \pm 0.29 \\ 1.91 & \pm 0.16 \\ 1.94 & \pm 0.33 \\ 2.22 & \pm 0.11 \\ \hline \textbf{35 days} \\ \hline \textbf{2.29} & \pm 0.15 \\ 2.43 & \pm 0.37 \\ 2.44 & \pm 0.37 \\ 2.44 & \pm 0.37 \\ 2.77 & \pm 0.28 \\ \end{array}$	Pvs Control nS nS nS nS Pvs Control nS NS * Pvs Control nS *	Pvs MDMA ns 	Pvs AMI+MDMA
Group A B C D Group A B C D Group A B C D D	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.32 Baseline Baseline 2.39 ± 0.43 2.91 ± 0.52 2.66 ± 0.25 2.69 ± 0.45	$\begin{array}{c} \textbf{14 days} \\ \textbf{1.64 } \pm 0.03 \\ \textbf{1.21 } \pm 0.18 \\ \textbf{1.51 } \pm 0.25 \\ \textbf{1.76 } \pm 0.24 \\ \hline \textbf{14 days} \\ \textbf{1.84 } \pm 0.01 \\ \textbf{1.84 } \pm 0.26 \\ \textbf{1.81 } \pm 0.29 \\ \textbf{2.12 } \pm 0.21 \\ \hline \textbf{14 days} \\ \textbf{2.15 } \pm 0.18 \\ \textbf{2.15 } \pm 0.18 \\ \textbf{2.92 } \\ \textbf{2.15 } \pm 0.18 \\ \textbf{2.92 } \\ \textbf{2.15 } \pm 0.18 \\ \textbf{2.93 } \pm 0.42 \\ \textbf{2.65 } \pm 0.28 \\ \textbf{2.95 } \pm 0.18 \\ \textbf{2.95 } \pm 0$	Pvs Control	Pus MDMA	Pvs AMI+MDMA	$\begin{array}{cccc} \textbf{21 days} \\ \textbf{1.61} & \textbf{$$ 0.20} \\ \textbf{1.24} & \textbf{$$ 0.28} \\ \textbf{1.20} & \textbf{$$ 0.62} \\ \textbf{1.76} & \textbf{$$ 0.32} \\ \hline \textbf{$$ 0.31} \\ \textbf{1.45} & \textbf{$$ 0.31} \\ \textbf{1.48} & \textbf{$$ 0.33} \\ \textbf{$$ 2.06} & \textbf{$$ 0.37} \\ \hline \textbf{$$ 0.32} \\ \textbf{$$ 2.05} & \textbf{$$ 0.30} \\ \textbf{$$ 2.52} & \textbf{$$ 0.30} \\ \textbf{$$ 2.55} & \textbf{$$ 0.30} \\ \textbf{$$ 2.55} & \textbf{$$ 0.38} \\ \textbf{$$ 0.38} \\ \textbf{$$ 0.38} \\ \textbf{$$ 0.55} & \textbf{$$ 0.39} \\ \textbf{$$ 0.56} & \textbf{$$ 0.39} \\ \textbf{$$ 0.56} & \textbf{$$ 0.38} \\ $$ 0.56$	Pvs Control	Pvs MDMA 	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA ns	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.13 1.62 ± 0.13 1.62 ± 0.13 1.50 ± 0.13 1.61 ± 0.13 1.62 ± 0.13 1.61 ± 0.13 1.62 ± 0.13 1.61 ± 0.13 1.62 ± 0.24 2.82 association 2.31 ± 0.25 2.35 ± 0.25 2.35 ± 0.25	Pvs Control 	Pvs MDMA # # ## ** ** ** ** ** ** ** ** ** ** **	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a ns	$\begin{array}{cccc} \textbf{35 days} \\ 1.50 & \pm 0.26 \\ 1.63 & \pm 0.11 \\ 1.71 & \pm 0.30 \\ 1.86 & \pm 0.31 \\ \hline \textbf{35 days} \\ 2.02 & \pm 0.29 \\ 1.91 & \pm 0.01 \\ 1.94 & \pm 0.33 \\ 2.22 & \pm 0.11 \\ \hline \textbf{35 days} \\ 2.29 & \pm 0.15 \\ 2.24 & \pm 0.07 \\ 2.43 & \pm 0.07 \\ 2.44 & \pm 0.37 \\ 2.77 & \pm 0.28 \\ \hline \textbf{35 days} \\ $	Pvs Control	Pvs MDMA	Pvs AMI+MDMA
Group A B C D A B C D B Group A B C D Group	ampusAnterc Control MDMA AMI+MDMA AMI+ Control MDMA AMI+MDMA AMI typothalamu: Control MDMA AMI+MDMA AMI+ MDMA AMI+ Thalamus	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35 Baseline 2.39 ± 0.43 2.91 ± 0.52 2.66 ± 0.25 2.69 ± 0.45 Baseline	$\begin{array}{r} \textbf{14 days} \\ \textbf{1.64 } \pm \textbf{0.03} \\ \textbf{1.21 } \pm \textbf{0.18} \\ \textbf{1.51 } \pm \textbf{0.25} \\ \textbf{1.76 } \pm \textbf{0.24} \\ \hline \textbf{14 days} \\ \textbf{1.84 } \pm \textbf{0.11} \\ \textbf{1.84 } \pm \textbf{0.12} \\ \textbf{1.81 } \pm \textbf{0.29} \\ \textbf{2.12 } \pm \textbf{0.21} \\ \hline \textbf{14 days} \\ \textbf{2.15 } \pm \textbf{0.18} \\ \textbf{1.92 } \pm \textbf{0.10} \\ \textbf{2.38 } \pm \textbf{0.42} \\ \textbf{2.65 } \pm \textbf{0.28} \\ \hline \textbf{14 days} \\ \hline \textbf{14 days} \end{array}$	Pvs Control	Pus MDMA	Pvs AMI+MDMA	$\begin{array}{c c c c c c c c } \hline 21 \ days \\ \hline 1.61 & \pm 0.20 \\ 1.24 & \pm 0.28 \\ 1.76 & \pm 0.29 \\ \hline \hline 21 \ days \\ \hline 2.06 & \pm 0.31 \\ 1.45 & \pm 0.23 \\ 2.06 & \pm 0.27 \\ \hline \hline 21 \ days \\ \hline 2.52 & \pm 0.43 \\ 2.55 & \pm 0.30 \\ 2.55 & \pm 0.38 \\ 2.55 & \pm 0.38 \\ \hline 2.5 & \pm 0.38 \\ \hline \end{array}$	Pvs Control	Pvs MDMA	Pvs AMI+MDMA Rvs AMI+MDMA Rvs AMI+MDMA ns Pvs AMI+MDMA Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.15 1.34 ± 0.15 1.62 ± 0.18 28 days 1.99 ± 0.09 1.61 ± 0.13 1.61 ± 0.13 1.61 ± 0.19 1.61 ± 0.24 28 days ± 0.25 2.31 ± 0.05 2.41 ± 0.25 2.08 ± 0.25 2.35 ± 0.37	Pvs Control 	Pvs MDMA	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a Pvs AMI+MDMA ns Pvs AMI+MDMA	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	Pvs Control NS NS NS NS Pvs Control NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS NS 	Pvs MDMA ns	Pvs AMI+MDMA
Group A B C D Group A B C D Group A B C D G G C D A	ampusAnterc Control MDMA AMI+MDMA AMI+ Control MDMA AMI+MDMA AMI Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+ Thalamus Control	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.32 Baseline 2.39 ± 0.43 2.94 ± 0.52 2.66 ± 0.25 2.69 ± 0.45 Baseline	$\begin{array}{r} 14 days \\ 1.64 \pm 0.03 \\ 1.21 \pm 0.18 \\ 1.51 \pm 0.25 \\ 1.76 \pm 0.24 \\ \hline \\ 14 days \\ 1.84 \pm 0.11 \\ 1.48 \pm 0.26 \\ 1.81 \pm 0.29 \\ 2.12 \pm 0.21 \\ 1.44 days \\ 2.15 \pm 0.18 \\ 1.92 \pm 0.10 \\ 2.15 \pm 0.18 \\ 1.92 \pm 0.10 \\ 2.15 \pm 0.18 \\ 1.92 \pm 0.10 \\ 2.15 \pm 0.14 \\ 1.94 \pm 0.04 \\ 2.55 \pm 0.28 \\ \hline \\ 1.94 \pm 0.04 \\ 1.94 \pm $	Pvs Control	Pvs MDMA # #### Pvs MDMA # #### Pvs MDMA fs #### Pvs MDMA Pvs MDMA	Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA	$\begin{array}{cccc} 21 \ days \\ 1.61 & \pm 0.20 \\ 1.24 & \pm 0.28 \\ 1.20 & \pm 0.62 \\ 1.76 & \pm 0.29 \\ \hline \\ 2.06 & \pm 0.31 \\ 1.45 & \pm 0.31 \\ 1.45 & \pm 0.32 \\ 2.06 & \pm 0.27 \\ \hline \\ 2.06 & \pm 0.23 \\ 2.05 & \pm 0.30 \\ \hline \\ 2.16 & \pm 0.32 \\ 2.55 & \pm 0.43 \\ 2.55 & \pm 0.4$	Pvs Control	Pvs MDMA ns # Pvs MDMA # # # # # # # # # # # # # # # ********	Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.10 1.33 ± 0.12 1.62 ± 0.13 1.50 ± 0.03 1.50 ± 0.13 1.50 ± 0.13 1.51 ± 0.19 1.99 ± 0.19 1.90 ± 0.24 2.31 ± 0.05 2.35 ± 0.37 2.35 ± 0.37 2.35 ± 0.37	Pvs Control	Pvs MDMA # # ## ## Pvs MDMA NS # Pvs MDMA Pvs MDMA	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a Pvs AMI+MDMA ns ns Pvs AMI+MDMA	35 days 1.50 ± 0.26 1.63 ± 0.11 1.71 ± 0.30 1.86 ± 0.31 35 days 2.02 ± 0.29 1.94 ± 0.33 2.22 ± 0.15 2.43 ± 0.07 2.29 ± 0.15 2.43 ± 0.07 2.77 ± 0.28 35 days 35 days	Pvs Control	Pvs MDMA 	Pvs AMI+MDMA
Group A B C D Group A B C D Group A B C D G Group A B C D C D C D C D C D C D C D C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C C D C C C D C	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI Thalamus Control MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.32 2.39 ± 0.43 2.39 ± 0.43 2.91 ± 0.52 2.66 ± 0.25 2.69 ± 0.45 2.03 ± 0.26 2.04 ± 0.64 2.03 ± 0.62	$\begin{array}{c} 14 \ days \\ 1.64 \ \pm 0.03 \\ 1.21 \ \pm 0.15 \\ 1.51 \ \pm 0.25 \\ 1.76 \ \pm 0.24 \\ \hline \\ 14 \ days \\ 1.84 \ \pm 0.11 \\ 1.48 \ \pm 0.26 \\ 1.81 \ \pm 0.29 \\ 2.12 \ \pm 0.21 \\ \hline \\ 14 \ days \\ 1.92 \ \pm 0.10 \\ 2.38 \ \pm 0.42 \\ 2.65 \ \pm 0.28 \\ 1.94 \ days \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ \hline \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ \hline \\ 1.52 \ \pm 0.26 \\ \hline \\ 1.94 \ \pm 0.08 \\ \hline \\ 1$	Pvs Control Current Pvs Control Current Curre	Pus MDMA	Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Pvs Control	Pvs MDMA ns # Pvs MDMA # # # Pvs MDMA # # # # # 	Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.15 1.62 ± 0.13 1.59 ± 0.03 1.50 ± 0.13 1.61 ± 0.13 1.62 ± 0.13 1.61 ± 0.19 1.99 ± 0.20 2.80 ± 0.02 2.31 ± 0.05 2.35 ± 0.32 2.34 ± 0.25 2.35 ± 0.32 2.36 ± 0.25 2.35 ± 0.32 2.36 ± 0.32 2.37 ± 0.32 2.38 ± 0.32 2.39 ± 0.32 2.30 ± 0.32 2.35 ± 0.34 4.43 ± 0.32	Pvs Control	Pvs MDMA # # # # # # Pvs MDMA Pvs MDMA	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a 	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Pvs Control	Pvs MDMA	Pvs AMI+MDMA
Group A B C D Group A B C D Group A C D Group A B C C D C C C C C C C C C C C C C C C C	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.13 1.66 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35 Baseline 2.39 ± 0.43 2.61 ± 0.25 2.66 ± 0.25 2.69 ± 0.45 Baseline 2.49 ± 0.64 2.47 ± 0.07	$\begin{array}{c} 14 \ days \\ 1.64 \ \pm 0.03 \\ 1.21 \ \pm 0.15 \\ \pm 0.25 \\ 1.76 \ \pm 0.24 \\ \hline \\ 1.84 \ \pm 0.01 \\ 1.84 \ \pm 0.01 \\ 1.84 \ \pm 0.02 \\ 2.12 \ \pm 0.21 \\ \hline \\ 1.84 \ \pm 0.29 \\ 2.12 \ \pm 0.21 \\ \hline \\ 1.84 \ \pm 0.29 \\ 2.15 \ \pm 0.18 \\ 1.92 \ \pm 0.10 \\ 2.38 \ \pm 0.42 \\ 2.65 \ \pm 0.28 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.28 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ 1.09 \ \pm 0.27 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.89 \ \pm 0.37 \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.89 \ \pm 0.37 \\ 1.94 \ \pm 0.08 \\ \hline \\ 1.52 \ \pm 0.246 \\ \hline \\ 1.89 \ \pm 0.37 \\ 1.94 \ \pm 0.08 \\ \hline \\ 1.52 \ \pm 0.246 \\ \hline \\ 1.89 \ \pm 0.37 \\ 1.94 \ \pm 0.08 \\ \hline \\ 1.52 \ \pm 0.246 \\ \hline \\ 1.89 \ \pm 0.37 \\ 1.94 \ \pm 0.08 \\ \hline \\ 1.94 \ \pm 0.04 \\$	Pvs Control	Pus MDMA 	Pvs AMI+MDMA	$\begin{array}{c c c c c c c } \hline 21 \ days \\ \hline 1.61 & \pm 0.20 \\ 1.24 & \pm 0.28 \\ 1.20 & \pm 0.62 \\ 1.76 & \pm 0.29 \\ \hline \hline 21 \ days \\ \hline 2.06 & \pm 0.31 \\ 1.45 & \pm 0.23 \\ 2.06 & \pm 0.27 \\ \hline \hline 21 \ days \\ \hline 2.50 & \pm 0.30 \\ 2.50 & \pm 0.30 \\ 2.50 & \pm 0.38 \\ \hline 2.50 & \pm 0.38 \\ \hline 2.50 & \pm 0.38 \\ \hline 2.10 & \pm 0.36 \\ \hline 2.10 & \pm 0.3$	Pvs Control 	Pvs MDMA 	Pvs AMI+MDMA	28 Jays 1.38 ± 0.15 1.32 ± 0.15 1.36 ± 0.15 1.62 ± 0.18 28 Jays 1.99 ± 0.09 1.50 ± 0.13 1.61 ± 0.13 1.61 ± 0.12 2.31 ± 0.02 2.31 ± 0.02 2.33 ± 0.25 2.35 ± 0.37 2.4 2.26 2.5 ± 0.12 1.41 ± 0.25 2.35 ± 0.37 2.40 ± 0.42 2.50 ± 0.12 1.61 ± 0.12 1.62 ± 0.12 1.67 ± 0.22	Pvs Control 	Pvs MDMA	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a Pvs AMI+MDMA ns Pvs AMI+MDMA 	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	Pvs Control NS NS NS NS NS NS NS NS NS NS NS 	Pvs MDMA ns	Pvs AMI+MDMA Pvs AMI+MDMA
Group A B C D Group A B C D Group A B C D G C D C D C D C D C C D C C D C C D C C D C C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C D C C C D C C C D C C C D C C C D C C D C C C D C C C D C C C D C C C D C C C D C C C C D C	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA	$\begin{tabular}{lllllllllllllllllllllllllllllllllll$	$\begin{array}{r} \textbf{14 days} \\ \textbf{1.64 } \pm 0.03 \\ \textbf{1.21 } \pm 0.18 \\ \textbf{1.51 } \pm 0.25 \\ \textbf{1.76 } \pm 0.24 \\ \hline \textbf{14 days} \\ \textbf{1.84 } \pm 0.11 \\ \textbf{1.48 } \pm 0.26 \\ \textbf{1.81 } \pm 0.29 \\ \textbf{2.12 } \pm 0.21 \\ \textbf{14 days} \\ \textbf{2.15 } \pm 0.18 \\ \textbf{1.92 } \pm 0.10 \\ \textbf{2.85 } \pm 0.28 \\ \hline \textbf{1.92 } \pm 0.10 \\ \textbf{2.65 } \pm 0.28 \\ \hline \textbf{1.94 } \pm 0.08 \\ \textbf{1.52 } \pm 0.24 \\ \hline \textbf{1.94 } \pm 0.08 \\ \textbf{1.52 } \pm 0.24 \\ \hline \textbf{1.94 } \pm 0.08 \\ \textbf{1.52 } \pm 0.24 \\ \hline \textbf{1.94 } \pm 0.37 \\ \hline \textbf{2.9 } \pm 0$	Pvs Control	Pvs MDMA # #### Pvs MDMA # #### Pvs MDMA # ####	Pvs AMI+MDMA	$\begin{array}{cccc} \textbf{21 days} \\ \textbf{1.61} & \textbf{2} & \textbf{0.20} \\ \textbf{1.24} & \textbf{i} & \textbf{0.28} \\ \textbf{1.20} & \textbf{i} & \textbf{0.62} \\ \textbf{1.76} & \textbf{i} & \textbf{0.29} \\ \hline \textbf{21 days} \\ \textbf{2.06} & \textbf{i} & \textbf{0.31} \\ \textbf{1.45} & \textbf{i} & \textbf{0.31} \\ \textbf{1.45} & \textbf{i} & \textbf{0.31} \\ \textbf{1.48} & \textbf{i} & \textbf{0.32} \\ \textbf{2.06} & \textbf{i} & \textbf{0.37} \\ \textbf{2.16} & \textbf{i} & \textbf{0.30} \\ \textbf{2.52} & \textbf{i} & \textbf{0.30} \\ \textbf{2.53} & \textbf{i} & \textbf{0.38} \\ \textbf{2.54} & \textbf{i} & \textbf{0.38} \\ \textbf{2.55} & \textbf{i} & \textbf{0.36} \\ \textbf{2.56} & \textbf{i} & \textbf{0.36} \\ \textbf{2.24} & \textbf{i} & \textbf{0.43} \end{array}$	Pvs Control	Pvs MDMA ns # Pvs MDMA # # # # # # # # # # #	Pvs AMI+MDMA	$\begin{array}{c c c c c c } \hline 28 \ \hbox{dusymmetry} \\ \hline 1.38 & \pm 0.15 \\ \hline 1.32 & \pm 0.01 \\ \hline 1.32 & \pm 0.15 \\ \hline 1.62 & \pm 0.13 \\ \hline 1.50 & \pm 0.13 \\ \hline 1.50 & \pm 0.13 \\ \hline 1.50 & \pm 0.14 \\ \hline 1.50 & \pm 0.25 \\ \hline 2.31 & \pm 0.06 \\ \hline 2.11 & \pm 0.25 \\ \hline 2.35 & \pm 0.37 \\ \hline 3.35 & \pm 0.35 \\ \hline 3.35 $	Pvs Control	Pvs MDMA 	Pvs AMI+MDMA ns M. Pvs AMI+MDMA a Pvs AMI+MDMA ns Pvs AMI+MDMA a a 	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	Pvs Control	Pvs MDMA ns ns ns ns Pvs MDMA ns # Pvs MDMA ns # Pvs MDMA ns # ns # ns # ns ns ns ns ns ns	Pvs AMI+MDMA
Group A B C D Group A B C D D Group A B C D G G C D D G F O D C D C D C D C D C D C D C D C D C D	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA AMI+MDMA AMI Control MDMA AMI Thalamus Control MDMA AMI MDMA AMI	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35 Baseline 2.39 ± 0.43 2.91 ± 0.52 2.66 ± 0.25 2.66 ± 0.25 2.66 ± 0.45 Baseline 2.03 ± 0.26 2.49 ± 0.64 2.07 ± 0.07 2.24 ± 0.35	$\begin{array}{c} 14 \ days \\ 1.64 \ \pm 0.03 \\ 1.21 \ \pm 0.12 \ \pm 0.25 \\ 1.76 \ \pm 0.24 \\ \hline \\ 14 \ days \\ 1.48 \ \pm 0.26 \\ 1.81 \ \pm 0.26 \\ 1.81 \ \pm 0.29 \\ 2.12 \ \pm 0.21 \\ \hline \\ 1.44 \ days \\ 1.45 \ \pm 0.10 \\ 2.38 \ \pm 0.42 \\ 2.65 \ \pm 0.28 \\ 1.45 \ days \\ 1.94 \ \pm 0.03 \\ 1.52 \ \pm 0.246 \\ 1.89 \ \pm 0.37 \\ 2.9 \ $	Pvs Control Rs Rs Rs Rs Rs Rs Rs Rs Rs R	Pvs MDMA # # #### #### #### #############	Pvs AMI+MDMA	$\begin{array}{c c c c c c c } \hline & 2 & 2.02 \\ \hline 1.54 & \pm 0.28 \\ 1.24 & \pm 0.28 \\ 1.20 & \pm 0.62 \\ 1.76 & \pm 0.29 \\ \hline \\ \hline \\ \hline \\ 2.06 & \pm 0.31 \\ 1.48 & \pm 0.31 \\ 1.48 & \pm 0.31 \\ 1.48 & \pm 0.32 \\ 2.06 & \pm 0.27 \\ \hline \\ \hline \\ \hline \\ 2.10 & \pm 0.38 \\ 2.50 & \pm 0.38 \\ 1.50 & \pm 0.30 \\ \hline \\ \hline \\ \hline \\ 2.10 & \pm 0.24 \\ 1.50 & \pm 0.36 \\ 2.24 & \pm 0.64 \\ 2.24 & \pm 0.48 \\ \hline \\ \end{array}$	Pvs Control	Pvs MDMA 	Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.42 ± 0.10 1.39 ± 0.13 1.62 ± 0.13 1.50 ± 0.13 1.50 ± 0.13 1.61 ± 0.13 1.62 ± 0.13 1.61 ± 0.13 1.62 ± 0.13 1.63 ± 0.24 28 days ± 0.25 2.31 ± 0.25 2.35 ± 0.37 2.36 ± 0.25 2.35 ± 0.37 2.36 ± 0.25 2.35 ± 0.37 2.36 ± 0.12 1.47 ± 0.12 1.67 ± 0.22 2.06 ± 0.12 1.67 ± 0.22 2.07 ± 0.24	Pvs Control	Pvs MDMA 	PVS AMI+MDMA ns M. PVS AMI+MDMA a a PVS AMI+MDMA ns PVS AMI+MDMA a a PVS AMI+MDMA a	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Pvs Control	Pvs MDMA ns ns ns ns ns # ns # ns # Pvs MDMA ns # ns ms ms ms ms ms ms ms ms ms	Pvs AMI+MDMA
Group A B C D B C D Group A B C D G C D C C D C C D C C D C C D C C D C	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA A	Baseline 1.56 ± 0.12 1.86 ± 0.13 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.31 2.23 ± 0.43 2.39 ± 0.43 2.66 ± 0.25 2.66 ± 0.25 2.69 ± 0.45 Baseline 2.03 ± 0.26 2.49 ± 0.64 2.07 ± 0.07 2.24 ± 0.35	$\begin{array}{r} 14 \ days \\ 1.64 \ \pm 0.03 \\ 1.21 \ \pm 0.15 \ \pm 0.25 \\ 1.76 \ \pm 0.24 \\ \hline \\ 1.84 \ \pm 0.01 \\ 1.84 \ \pm 0.01 \\ 1.84 \ \pm 0.02 \\ 2.12 \ \pm 0.21 \\ \hline \\ 1.48 \ \pm 0.29 \\ 2.12 \ \pm 0.21 \\ \hline \\ 1.48 \ \pm 0.29 \\ 2.15 \ \pm 0.18 \\ 1.92 \ \pm 0.10 \\ 2.38 \ \pm 0.42 \\ 2.65 \ \pm 0.28 \\ \hline \\ 1.44 \ days \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.28 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ 1.89 \ \pm 0.37 \\ 2.29 \ \pm 0.37 \\ \hline \\ 1.94 \ days \\ 2.09 \ \pm 0.07 \\ \hline \\ 2.09 \ \pm 0.07 \\ \hline \\ 1.94 \ days \\ 1.94 \ day$	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Pvs Control	Pvs MDMA NS # Pvs MDMA # # # Pvs MDMA # # # Pvs MDMA	Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.01 1.39 ± 0.15 1.62 ± 0.18 28 days 1.59 ± 0.01 1.50 ± 0.13 1.61 ± 0.13 1.61 ± 0.12 2.31 ± 0.02 2.31 ± 0.02 2.35 ± 0.37 2.35 ± 0.12 2.06 ± 0.12 2.06 ± 0.12 1.49 ± 0.12 1.47 ± 0.22 2.02 ± 0.12 1.49 ± 0.22 2.02 ± 0.23	Pvs Control Pvs Control	Pvs MDMA # ## ## ## Pvs MDMA # ## ## ## ## Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA a Pvs AMI+MDMA ns Pvs AMI+MDMA a Pvs AMI+MDMA a	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	Pvs Control	Pvs MDMA ns	Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA
Group A B C D Group A B C C D Group A B C D D Group A B C D D Group A B C D D C D C D C C C C C D C	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA	$\begin{tabular}{lllllllllllllllllllllllllllllllllll$	$\begin{array}{r} 14 days \\ 1.64 \ \pm 0.03 \\ 1.21 \ \pm 0.13 \\ 1.51 \ \pm 0.25 \\ 1.76 \ \pm 0.24 \\ \hline \\ 14 days \\ 1.84 \ \pm 0.11 \\ 1.48 \ \pm 0.26 \\ 1.81 \ \pm 0.29 \\ 2.12 \ \pm 0.21 \\ \hline \\ 1.44 days \\ 2.15 \ \pm 0.28 \\ \hline \\ 1.92 \ \pm 0.10 \\ 2.38 \ \pm 0.42 \\ 2.65 \ \pm 0.28 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.24 \\ \hline \\ 1.94 \ \pm 0.03 \\ 1.94 \ \pm 0.03 \\ \hline \\ 1.94 \ \pm 0.03 \\ 1.94 \ \pm 0.03 \\ \hline \\ 1.94 \ \pm 0.03$	Pvs Control C	Pvs MDMA	Pvs AMI+MDMA	$\begin{array}{cccc} 21 \ days \\ 1.61 & \pm 0.20 \\ 1.24 & \pm 0.28 \\ 1.20 & \pm 0.62 \\ 1.76 & \pm 0.29 \\ \hline \\ 2.06 & \pm 0.31 \\ 1.45 & \pm 0.31 \\ 1.45 & \pm 0.31 \\ 1.48 & \pm 0.23 \\ 2.06 & \pm 0.27 \\ \hline \\ 2.10 \ starting to the starting term \\ \hline \\ 2.52 & \pm 0.43 \\ 2.55 & \pm 0.43 \\ 2.55 & \pm 0.43 \\ \hline \\ 2.50 & \pm 0.30 \\ \hline \\ 2.10 \ starting term \\ \hline \\ 2.10 \ starting term \\ 2.10 \ starting term \\ \hline \\ 2.10 \ starting term \\ 2.10 \ starting term \\ \hline \\ 2.10 \ starting term \\ 2.10 \ starting term \\ \hline \\ 2.10 \ startin$	Pvs Control	Pvs MDMA ns # Pvs MDMA # # # # # # # # # # # # # # # # # # # # # # # # * * * * * * * * * * * * *	Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.01 1.33 ± 0.15 1.62 ± 0.13 1.50 ± 0.13 1.50 ± 0.13 1.50 ± 0.13 1.51 ± 0.19 1.90 ± 0.24 2.31 ± 0.06 2.31 ± 0.05 2.35 ± 0.37 2.35 ± 0.37 2.35 ± 0.32 2.35 ± 0.22 2.06 ± 0.14 1.49 ± 0.12 2.06 ± 0.14 1.49 ± 0.12 2.02 ± 0.28 2.02 ± 0.28 2.02 ± 0.28 2.18 ± 0.19	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	Pvs Control	Pvs MDMA ns ns ns Pvs MDMA ns # Pvs MDMA ns # ns # ns # ns	Pvs AMI+MDMA
Group A B C D C D A B C C D C C C C C C C C C C C C C C C C	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI Thalamus Control MDMA AMI+MDMA AMI Control MDMA AMI	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.86 ± 0.31 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35 Baseline 2.39 ± 0.43 2.39 ± 0.42 2.66 ± 0.25 2.66 ± 0.25 2.66 ± 0.42 2.03 ± 0.26 2.49 ± 0.64 2.07 ± 0.07 2.24 ± 0.35 Baseline 2.09 ± 0.03 2.09 ± 0.03 2.09 ± 0.03 2.09 ± 0.03	$\begin{array}{r} 14 \ days \\ 1.64 \ \pm 0.03 \\ 1.21 \ \pm 0.15 \\ 1.51 \ \pm 0.25 \\ 1.76 \ \pm 0.24 \\ \hline \\ 14 \ days \\ 1.84 \ \pm 0.21 \\ 1.81 \ \pm 0.26 \\ 1.81 \ \pm 0.29 \\ 2.12 \ \pm 0.21 \\ \hline \\ 14 \ days \\ 2.15 \ \pm 0.10 \\ 2.38 \ \pm 0.42 \\ 2.65 \ \pm 0.28 \\ 1.92 \ \pm 0.10 \\ 2.38 \ \pm 0.42 \\ 2.65 \ \pm 0.28 \\ \hline \\ 1.40 \ days \\ 1.94 \ \pm 0.08 \\ 1.52 \ \pm 0.246 \\ 1.89 \ \pm 0.37 \\ 2.99 \ \pm 0.03 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.90 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 1.85 \ \pm 0.28 \\ 1.85 \ \pm$	Pvs Control Pvs Control Pvs C	Pvs MDMA # # #### Pvs MDMA # # #### Pvs MDMA B # #### Pvs MDMA B # #### Pvs MDMA B # ####	Pvs AMI+MDMA	$\begin{array}{cccc} 21 \ days \\ 1.61 & \pm 0.20 \\ 1.24 & \pm 0.28 \\ 1.20 & \pm 0.62 \\ 1.76 & \pm 0.29 \\ \hline \\ \hline \\ 2.06 & \pm 0.31 \\ 1.48 & \pm 0.23 \\ 2.06 & \pm 0.31 \\ 1.48 & \pm 0.23 \\ 2.06 & \pm 0.27 \\ \hline \\ \hline \\ 2.10 & \pm 0.43 \\ 2.05 & \pm 0.30 \\ 2.38 & \pm 0.89 \\ 2.50 & \pm 0.38 \\ \hline \\ 2.10 & \pm 0.43 \\ 2.10 & \pm 0.43 \\ 2.50 & \pm 0.30 \\ 1.98 & \pm 0.36 \\ 2.10 & \pm 0.24 \\ 1.50 & \pm 0.30 \\ 1.98 & \pm 0.36 \\ 2.24 & \pm 0.43 \\ 1.50 & \pm 0.31 \\ 1.98 & \pm 0.36 \\ 2.24 & \pm 0.43 \\ 1.90 & \pm 0.36 \\ 1.90$	Pvs Control	Pvs MDMA 	Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.10 1.39 ± 0.12 1.62 ± 0.18 28 days 1.59 ± 0.19 1.50 ± 0.13 1.61 ± 0.19 1.62 ± 0.24 2.82 days 2.32 2.31 ± 0.60 2.35 ± 0.32 2.36 ± 0.25 2.35 ± 0.32 2.35 ± 0.32 2.36 ± 0.12 1.67 ± 0.22 2.06 ± 0.22 2.02 ± 0.28 2.04 ± 0.12 1.67 ± 0.22 2.02 ± 0.28 2.18 ± 0.19 1.78 ± 0.22	Pvs Control	Pvs MDMA "" " " " " " " " " " " " " " " " " "	Pvs AMI+MDMA Ins Ins Ins Pvs AMI+MDMA Ins Ins Pvs AMI+MDMA Ins Ins Pvs AMI+MDMA Ins Ins Pvs AMI+MDMA Ins Ins	$\begin{array}{rrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrrr$	Pvs Control	Pvs MDMA ns ns ns ns ns Pvs MDMA	Pvs AMI+MDMA
Group A B C D Group A B C D Group A B C D D Group A B C D D Group	ampusAnterc Control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA AMI Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA	Baseline 1.56 ± 0.12 1.86 ± 0.31 1.63 ± 0.15 1.75 ± 0.20 Baseline 1.96 ± 0.27 2.24 ± 0.30 2.13 ± 0.11 2.23 ± 0.35 Baseline 2.39 ± 0.43 2.94 ± 0.52 2.66 ± 0.25 2.69 ± 0.45 Baseline 2.03 ± 0.26 2.49 ± 0.64 2.07 ± 0.07 2.24 ± 0.35 Baseline 2.09 ± 0.03 2.05 ± 0.17 2.28 ± 0.37 2.05 ± 0.17 2.28 ± 0.37	$\begin{array}{r} 14 days \\ 1.64 \ \pm 0.03 \\ 1.21 \ \pm 0.18 \\ 1.51 \ \pm 0.25 \\ 1.76 \ \pm 0.24 \\ \hline \\ 14 days \\ 1.48 \ \pm 0.11 \\ 1.48 \ \pm 0.26 \\ 1.81 \ \pm 0.29 \\ 2.12 \ \pm 0.21 \\ 2.12 \ \pm 0.21 \\ 2.15 \ \pm 0.18 \\ 1.92 \ \pm 0.42 \\ 2.65 \ \pm 0.42 \\ 2.65 \ \pm 0.42 \\ 1.94 \ \pm 0.03 \\ 1.94 \ \pm 0.03 \\ 1.52 \ \pm 0.37 \\ 2.29 \ \pm 0.37 \\ 2.29 \ \pm 0.37 \\ 2.29 \ \pm 0.37 \\ 1.46 days \\ 1.5 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.09 \ \pm 0.03 \\ 1.75 \ \pm 0.27 \\ 2.03 \ \pm 0.27 \\ 2.04 \ \pm 0.27 \\ 2.04 \ \pm 0.27 \\ 2.05 \ \pm 0.27 $	Pvs Control S S S S S S S S S S S S S S S S S S	Pvs MDMA # #### Pvs MDMA # #### Pvs MDMA fill### Pvs MDMA # ##### Pvs MDMA # ##### Pvs MDMA # ####################################	Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA	$\begin{array}{c c c c c c } \hline & 21 \ days \\ \hline 1.61 & \pm 0.20 \\ 1.24 & \pm 0.28 \\ 1.20 & \pm 0.62 \\ 1.76 & \pm 0.29 \\ \hline \\ \hline & 21 \ days \\ \hline & 2.06 & \pm 0.31 \\ 1.45 & \pm 0.31 \\ 1.45 & \pm 0.31 \\ 1.48 & \pm 0.23 \\ \hline & 2.06 & \pm 0.32 \\ \hline & 2.06 & \pm 0.31 $	Pvs Control	Pvs MDMA RS # Pvs MDMA # # # Pvs MDMA # # # Pvs MDMA # # Pvs MDMA	Pvs AMI+MDMA	28 days 1.38 ± 0.15 1.32 ± 0.15 1.62 ± 0.18 1.99 ± 0.013 1.50 ± 0.13 1.61 ± 0.19 1.99 ± 0.02 1.90 ± 0.02 2.01 ± 0.02 2.01 ± 0.02 2.02 ± 0.22 2.05 ± 0.14 1.49 ± 0.22 2.02 ± 0.22 2.02 ± 0.22 2.02 ± 0.22 2.02 ± 0.22 2.02 ± 0.22 2.16 ± 0.12 2.18 ± 0.12 2.18 ± 0.12 2.18 ± 0.12 2.18 ± 0.22 2.18 ± 0.22 2.18 ± 0.22 2.18 ± 0.22 2.18 ± 0.22 2.18 ± 0.22 2.18 ± 0.22 2.18 ± 0.22 2.14	Pvs Control	Pvs MDMA # # ## ## Pvs MDMA ns # # ## ## Pvs MDMA # # ## ## ## ## ## ## ## ## ## ## #	Pvs AMI+MDMA Ins	$\begin{array}{cccc} 35 days \\ 1.50 & \pm 0.26 \\ 1.63 & \pm 0.11 \\ 1.71 & \pm 0.30 \\ 1.86 & \pm 0.31 \\ \hline \\ 35 days \\ 2.02 & \pm 0.29 \\ 1.91 & \pm 0.16 \\ 1.94 & \pm 0.33 \\ 2.22 & \pm 0.11 \\ 35 days \\ \hline \\ 2.29 & \pm 0.15 \\ 2.43 & \pm 0.07 \\ 2.77 & \pm 0.28 \\ \hline \\ 35 days \\ 1.98 & \pm 0.31 \\ 1.91 & \pm 0.10 \\ 1.97 & \pm 0.33 \\ 2.32 & \pm 0.49 \\ \hline \\ 35 days \\ 2.03 & \pm 0.16 \\ 1.97 & \pm 0.33 \\ 2.32 & \pm 0.49 \\ \hline \\ 35 days \\ 2.03 & \pm 0.16 \\ 0.04 & \pm 0.05 \\ 2.22 & \pm 0.27 \\ 2.03 & \pm 0.05 \\ 2.22 & \pm 0.05 \\ 2.24 & \pm$	Pvs Control	Pvs MDMA	Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA Pvs AMI+MDMA

Figure 4. Specific uptake ratios (SURs) of 4-[¹⁸F]-ADAM in 9 brain areas under different drug treatments from day 0 to day 35. Data are mean \pm SD. Animals were grouped into (1) Group A: saline control; (2) Group B: MDMA; (3) Group C: AMI with MDMA; or (4) Group D: AMI alone. Different superscript symbols denote difference level of significance (red * p < 0.05, ** p < 0.01, *** p < 0.005 Group B or C or D vs. Group A; blue # p < 0.05, ## p < 0.01, ### p < 0.005, Group A or C or D vs. Group B; a p < 0.05, Group A or B or D vs. Group C, aa p < 0.01, ns = not significant).

This shows the 4-[¹⁸F]-ADAM distribution in the different brain regions after intraperitoneal administration of different drug groups. Compared to the control (black line), MDMA produced a significant reduction of 4-[¹⁸F]-ADAM binding to SERT from day 14, and progressively increased up to day 35 (red line). In all brain regions, the SURs in the MDMA group significantly decreased up to day 28 (red * p < 0.05~*** p < 0.0001, Group B-MDMA compared to Group A-control) and returned to baseline at day 35 (Figure 3 red line).

The group of AMI with MDMA (Figure 3 blue line) showed the neuroprotective effect from day 14, with statistical differences with the MDMA group (blue # p < 0.05~## p < 0.01 Group C-AMI+MDMA compared to Group B-MDMA). The AMI alone (Figure 3 green line) group showed a similar pattern with the control (Figure 3 black line). Detailed statistical results between groups are summarized in Figure 4.

After normalizing to the baseline value, we calculated the SERT recovery rate (% percentage) at each time point. Figure 5 showed that the recovery rate of the control group remained relatively flat (black line), whereas the MDMA group (red line) appeared at its lowest recovery rate at day 14 (71.29% \pm 3.21%) and slightly increased at day 21 (74.38% \pm 1.62%), day 28 (75.58% \pm 7.87%), and day 35 (90.90% \pm 7.63%). According to the SERT recovery rate, from day 14 to day 35, brain regions of the MDMA group averagely divided into three classifications: Low recovery rate (61~69%): thalamus, hypothalamus, hippocampus posterior, hippocampus anterodorsal and cingulate cortex; mid recovery rate (71%~79%): striatum, auditory cortex, and motor cortex; and high recovery rate (80%~90%): visual cortex and midbrain. Detailed statistical results between each group are summarized in Figure 6.



Figure 5. Comparison of recovery rate, based on graphical analyses of 4-[¹⁸F]-ADAM binding before and after drug administration. Among four groups, the MDMA group (red line) showed the lowest recovery rate at day 14, slightly increased at day 21, and recovered to ~70% of baseline value at day 35 (red line and red * p < 0.05, *** p < 0.005, Group B-MDMA vs. Group A-control). MDMA with AMI pre-treatment significantly accelerated the recovery rate from day 14 and slowly increased up to day 35 when compared with the MDMA group (blue line and blue # p < 0.05, ## p < 0.01, ### p < 0.005, Group C-MDMA+AMI vs. Group B-MDMA). The control and AMI alone (green line) groups showed similar pattern in recovery rate. Data are mean \pm SD. Detailed statistical results between each group are summarized in Figure 6.

Group	Striatum	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days	Pvs Control	Pvs MDMA P	vs AMI+MDMA
A	Control	100.00%	96.14% ± 3.43%				102.65% ± 11.50%				100.42% ± 14.76%				94.21% ± 9.07%			
В	MDMA	100.00%	72.92% ± 8.45%	***			78.96% ± 8.57%				84.66% ± 17.92%				96.66% ± 3.32%	ns		
С	AMI+MDMA	100.00%	87.76% ± 4.93%	***	###		93.93% ± 8.55%	ns	#		89.35% ± 12.32%	ns	#		102.92% ± 4.34%	ns	ns	
D	AMI	100.00%	94.80% ± 6.83%	ns	#####		92.15% ± 8.70%	ns	##	ns	90.27% ± 12.38%	ns	#	ns	97.03% ± 14.36%	ns		ns
Group	uditoryCorte	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days	Pvs Control	Pvs MDMA P	vs AMI+MDMA
A	Control	100.00%	105.7% + 3.9%				103.3% + 11.0%				103.3% + 11.0%				112.9% + 21.4%			
R	MDMA	100.00%	72 92% + 8 45%	***			79 49% + 6 25%				78 34% + 3 23%	***			91 70% + 14 86%	ns		
-		100.00%	84.67% + 9.56%				86 73% + 10 80%				80 90% + 7 20%		ns		08.01% + 17.33%		ns	
D	ΔΜΙ	100.00%	91 64% + 11 09%			а	97 79% + 12 26%		#	а	89 18% + 10 87%	ns	#	ns	99 93% + 15 62%	ns		ns
	/	100.0070	51.0470 2 11.0570			ŭ	57.7570 2 12.2070			ŭ	05.1070 1 10.0270	115		115	55.5570 2 25.0270	115		115
Group	ngulateCorte	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pus AMI+MDMA	35 days	Pvs Control		vs AMI+MDMA
	Control	100.00%	92 9% + 7 7%				102 72% + 6 97%				103 22% + 14 28%				99 19% + 11 70%			
R	MDMA	100.00%	65 54% + 7 68%	***			73 86% + 9 67%	***			71 80% + 5 65%	***			89 37% + 7 37%	ns		
c		100.00%	97.95% + 16.01%	- DE			88 46% ± 13 07%				81 30% + 5 07%				9/ 13% + 16 60%	113	ns	
D		100.00%	07 120 ± 0.01%	nc 113			01.67% ± 0.25%			25	02.44% ± 0.42%			-	101.06% ± 7.60%	113	113	
	Aivii	100.00%	57.12/0 ± 5.47/0	115		115	91.07% ± 9.33%	115	***	115	52.44% ± 5.42%	115		d	101.00% ± 7.05%	115	115	115
Group	MotorCortox	Pacolino	14 days	Pur Control	Duc MDMA		21 days	Buc Control			28 days	Bur Control		Die ANALINADAAA	2E dave	Buc Control		
Group	Control	100.00%	07 61% ± 2 55%	PVS CONTION	PVSIVIDIVIA	PVS AIVITTIVIDIVIA	105 47% ± 6 52%	FVS CONTION	PVS WIDWA	PVS AIVIITIVIDIVIA	102 11% ± 0 76%	PVS CONTION	PVS WIDWA	-VS AIVIITIVIDIVIA	109 90% ± 17 02%	PVS CONTION	PVS IVIDIVIA P	VS AIVIITIVIDIVIA
ĥ	MDMA	100.00%	74 15% + 10 57%	***			81 10% + 0.02%	***			79.81% + 5.65%	***			05.81% + 6.15%	ns		
c		100.00%	96 71% ± 10 70%	· *			97 119/ ± 5.05%	**			92 749/ ± 5 079/		86		01 77% ± 0.22%	113		
		100.00%	07 110 + 6 650			-	0F 0F 0 + 0.50%		#	-	07.66% ± 7.00%		115	-	06 01% ± 13 03%	115	115	20
	Aivii	100.00%	97.11% ± 0.03%	115		d	53.53% ± 8.07%	115	#	d	57.00% ± 7.00%	115		d	50.51% ± 15.02%	115	115	115
Group	VisualCortox	Pacolino	14 days	Bur Control	Duc MDMA		21 days	Buc Control		A Duc AAAI	28 days	Due Control			2E dave	Buc Control		Duc AMI
Group	Cantan	100.00%	101.000 L 5.2200	PVS CONTION	PVSIVIDIVIA	FVS AIVIITIVIDIVIA	101 050(L 2 050)	PVS CONTION	VS AIVITTIVIDIVI	A FVS AIVII	20 uays	PVS CONTION	VS AIVIIŦIVIDIV	FVS AIVII	100 73% L C 10%	PVS CONTION	75 AIVITTIVIDIVI.	PVS AIVII
A	Control	100.00%	101.80% ± 5.22%	***			101.95% I 2.06%	*			102.21% ± 11.10%	*			100.72% ± 0.19%			
в	MDMA	100.00%	83.15% ± 5.82%				85.81% ± 9.92%				88.42% ± 9.68%				99.52% ± 14.80%	ns		
C	AMI+MDMA	100.00%	89.87% ± 11.67%	5 ns	#		91.69% ± 7.40%	ns	ns		94.59% ± 8.64%	ns	ns		107.77% ± 13.36%	ns	ns	
D	AMI	100.00%	99.97% ± 8.55%	ns	###	ns	100.80% ± 6.59%	•	#	а	99.73% ± 8.51%	ns	#	ns	111.16% ± 9.88%	ns	ns	ns
C		Desellers	14 4	Due Control	0		21 days	Due Control	0		20 dava	Due Control	0	Due 444/1400444	25 dava	Due Contral	0	
Group	ampusAnter	Baseline	14 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	² vs AMI+MDMA	35 days	Pvs Control	Pvs MDMA P	vs AMI+MDMA
Group A	3mpusAnter Control	Baseline 100.00%	14 days 105.12% ± 1.72%	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days 103.27% ± 2.06%	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days 105.84% ± 25.95%	Pvs Control	Pvs MDMA P	vs AMI+MDMA
Group A B	ampusAnter Control MDMA	Baseline 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69%	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10%	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days 103.11% ± 10.89% 71.04% ± 5.22%	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15%	Pvs Control	Pvs MDMA P	vs AMI+MDMA
Group A B C	ampusAnter Control MDMA AMI+MDMA	Baseline 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78%	Pvs Control	Pvs MDMA 	Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88%	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06%	Pvs Control **** *	Pvs MDMA	Pvs AMI+MDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78%	Pvs Control ns ns	Pvs MDMA P	
Group A B C D	ampusAnteri Control MDMA AMI+MDMA AMI	Baseline 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66%	Pvs Control **** ns *	Pvs MDMA ####	Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85%	Pvs Control	Pvs MDMA ### ##	Pvs AMI+MDMA ns	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02%	Pvs Control	Pvs MDMA ###	Pvs AMI+MDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26%	Pvs Control ns ns ns	Pvs MDMA P	vs AMI+MDMA ns
Group A B C D	ampusAnteri Control MDMA AMI+MDMA AMI	Baseline 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66%	Pvs Control	Pvs MDMA	Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85%	Pvs Control	Pvs MDMA	Pvs AMI+MDMA ns	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02%	Pvs Control *** * ns	Pvs MDMA	Pvs AMI+MDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26%	Pvs Control	Pvs MDMA P	vs AMI+MDMA ns
Group A C D Group	ampusAnteri Control MDMA AMI+MDMA AMI ocampusPost	Baseline 100.00% 100.00% 100.00% 100.00% Baseline	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days	Pvs Control	Pvs MDMA #### ##### Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days	Pvs Control *** ns * Pvs Control	Pvs MDMA #### ### Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days	Pvs Control	Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days	Pvs Control ns ns ns Pvs Control	Pvs MDMA P ns ns Pvs MDMA P	ns Nys AMI+MDMA
Group A B C D Group A	ampusAnteri Control MDMA AMI+MDMA AMI ocampusPost Control	Baseline 100.00% 100.00% 100.00% Baseline 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.22% ± 5.83%	Pvs Control Pvs Control Pvs Control Pvs Control	Pvs MDMA #### ##### Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21%	Pvs Control ns * Pvs Control	Pvs MDMA #### ## Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43%	Pvs Control	Pvs MDMA #### #### Pvs MDMA	≥vs AMI+MDMA ns ≥vs AMI+MDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35%	Pvs Control ns ns Pvs Control 	Pvs MDMA P ns ns Pvs MDMA P 	ns
Group A B C D Group A B	ampusAnteri Control MDMA AMI+MDMA AMI control MDMA	Baseline 100.00% 100.00% 100.00% 100.00% Baseline 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 5.83% 59.99% ± 10.49%	Pvs Control	Pvs MDMA #### ##### Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75%	Pvs Control	Pvs MDMA ### ## Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA 	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 59.31% ± 11.85%	Pus Control	Pvs MDMA #### #### Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA 	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44%	Pvs Control	Pvs MDMA P ns ns Pvs MDMA P 	vs AMI+MDMA ns vs AMI+MDMA
Group A C D Group A B C	ampusAnteri Control MDMA AMI+MDMA AMI compusPost Control MDMA AMI+MDMA	Baseline 100.00% 100.00% 100.00% 00.00% 100.00% 00.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 5.83% 59.99% ± 10.49% 82.88% ± 14.01%	Pvs Control	Pvs MDMA #### Pvs MDMA ####	Pvs AMI+MDMA ns Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20%	Pvs Control ns *** Pvs Control **** *	Pvs MDMA ### Pvs MDMA ###	Pvs AMI+MDMA ns Pvs AMI+MDMA 	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 59.31% ± 11.85% 75.46% ± 9.03%	Pvs Control Pvs Control 	Pvs MDMA ### ### Pvs MDMA ##	Pvs AMI+MDMA ns Pvs AMI+MDMA 	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44% 90.96% ± 15.47%	Pvs Control ns ns Pvs Control Pvs Control ns ns ns	Pvs MDMA P ns ns Pvs MDMA P ns	ns
Group A C D Group A B C D	ampusAnteri Control MDMA AMI+MDMA AMI Control MDMA AMI+MDMA AMI	Baseline 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 5.83% 9.99% ± 10.49% 22.88% ± 14.01% 92.71% ± 5.94%	Pvs Control	Pvs MDMA ### #### Pvs MDMA #### ####	Pvs AMI+MDMA ns Pvs AMI+MDMA a	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20% 85.29% ± 7.12%	Pvs Control ns Pvs Control + + + + + + + + + + + +	Pvs MDMA ### ## Pvs MDMA ### ## ## ## ## ## ## ## ## ## ##	Pvs AMI+MDMA ns Pvs AMI+MDMA ns	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 59.31% ± 11.85% 75.46% ± 9.03% 91.70% ± 10.92%	Pvs Control ns Pvs Control ns	Pvs MDMA ### ###	Pvs AMI+MDMA ns Pvs AMI+MDMA ns ns	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44% 90.96% ± 15.47% 98.60% ± 5.10%	Pvs Control ns ns Pvs Control Pvs Control ns ns ns ns ns ns ns	Pvs MDMA P ns ns Pvs MDMA P ns ##	ns ns ns ns ns ns
Group A B C D Group A B C D	3mpusAnteri Control MDMA AMI+MDMA AMI Control MDMA AMI+MDMA AMI	Baseline 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 5.83% 59.99% ± 10.49% 82.88% ± 14.01% 92.71% ± 5.94%	Pvs Control ns *** Pvs Control *** ns ns ns ns ns ns ns ns ns	Pvs MDMA #### ##### Pvs MDMA #### #####	Pvs AMI+MDMA ns Pvs AMI+MDMA a	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20% 85.25% ± 7.12%	Pvs Control	Pvs MDMA ### ## Pvs MDMA ### ## ##	Pvs AMI+MDMA ns Pvs AMI+MDMA ns	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 59.31% ± 11.85% 75.46% ± 9.03% 91.70% ± 10.92%	Pvs Control +*** ns Pvs Control *** ns	Pvs MDMA #### Pvs MDMA # # ###	-vs AMI+MDMA ns -vs AMI+MDMA ns	35 days 105.84% ± 25.95% 87.69% ± 25.95% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44% 90.96% ± 15.47% 98.60% ± 5.10%	Pvs Control ns ns ns Pvs Control ns ns ns	Pvs MDMA P ns Pvs MDMA P ns ##	vs AMI+MDMA ns vs AMI+MDMA ns
Group A B C D Group A B C D Group	ampusAnteri Control MDMA AMI+MDMA AMI control MDMA AMI+MDMA AMI Iypothalamu	Baseline 100.00% 100.00% 100.00% 100.00% Baseline 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 5.83% 59.99% ± 10.49% 82.88% ± 10.49% 82.71% ± 5.94% 14 days 14 days	Pvs Control	Pvs MDMA ### #### Pvs MDMA #### #### #### ###### Pvs MDMA #### ####################################	Pvs AMI+MDMA ns Pvs AMI+MDMA a Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20% 85.29% ± 7.12% 21 days	Pus Control	Pvs MDMA ### ## Pvs MDMA ### ## Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA	28 days 103.11% ± 10.8% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 59.31% ± 11.85% 75.46% ± 9.03% 91.70% ± 10.92% 28 days	Pvs Control	Pvs MDMA ### Pvs MDMA # # ### Pvs MDMA	Pys AMI+MDMA ns Pys AMI+MDMA ns Ns Pys AMI+MDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44% 90.96% ± 15.47% 98.60% ± 5.10% 35 days	Pvs Control	Pvs MDMA P ns ns Pvs MDMA P Pvs MDMA P	ns ns vs AMI+MDMA ns vs AMI+MDMA vs AMI+MDMA
Group A C D Group A C D Group	ampusAnteri Control MDMA AMI+MDMA AMI control MDMA AMI+MDMA AMI Iupothalamu Control	Baseline 100.00% 100.00% 100.00% 100.00% Baseline 100.00% 100.00% 100.00% Baseline 100.00% 100.00% 100.00% 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 5.83% 59.99% ± 10.49% 82.88% ± 10.40% 92.71% ± 5.94% 93.44% ± 5.83%	Pvs Control	Pvs MDMA Pvs MDMA #### ##### Pvs MDMA #### #####	Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20% 51.29% ± 7.21%	Pvs Control	Pvs MDMA #### ## Pvs MDMA ## ### Pvs MDMA ## ### Pvs MDMA	Pvs AMIHMDMA ns Pvs AMIHMDMA ns Pvs AMIHMDMA	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 10.85% 75.46% ± 9.03% 91.70% ± 10.92% 28 days 101.57% ± 2.68%	Pvs Control	Pvs MDMA #### Pvs MDMA # ### Pvs MDMA	Pus AMHHDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44% 90.96% ± 15.47% 98.60% ± 5.10% 35 days 93.53% ± 6.29%	Pvs Control ns ns ns Pvs Control ns ns Pvs Control Pvs Control 	Pvs MDMA P ns ns Pvs MDMA P ns ### Pvs MDMA P	vs AMIHMDMA ns vs AMIHMDMA ns vs AMIHMDMA
Group A B C D Group A B C D Group A B	ampusAnteri Control MDMA AMI+MDMA AMI control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA	Baseline 100.00% 100.00% 100.00% 100.00% Baseline 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 5.83% 59.99% ± 10.49% 82.88% ± 10.49% 82.88% ± 10.49% 92.71% ± 5.94% 14 days 93.44% ± 5.83% 61.20% ± 9.89%	Pvs Control The second	Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA a Pvs AMI+MDMA 	21 days 103.27% ± 2.05% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20% 85.29% ± 7.12% 21 days 105.23% ± 7.21% 68.53% ± 7.21%	Pvs Control ns Pvs Control	Pvs MDMA ### ## Pvs MDMA ## ## Pvs MDMA ## ## Pvs MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 75.46% ± 9.03% 91.70% ± 10.92% 28 days 101.57% ± 2.68% 68.15% ± 8.54%	Pus Control 	Pvs MDMA #### Pvs MDMA # ### Pvs MDMA	avs AMI+MDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44% 90.96% ± 15.47% 98.60% ± 5.10% 35 days 93.53% ± 6.29% 83.47% ± 3.34%	Pvs Control ns ns Pvs Control ns ns Pvs Control Pvs Control ns ns	Pvs MDMA P ns ns Pvs MDMA P NS ## Pvs MDMA P	ns ns vs AMI+MDMA ns vs AMI+MDMA vs AMI+MDMA
Group A B C D Group A B C D Group A B C	impusAnteri Control MDMA AMI+MDMA AMI control MDMA AMI+MDMA AMI+ Control MDMA AMI+MDMA	Baseline 100.00% 100.00% 100.00% 100.00% Baseline 100.00% 100.00% Baseline 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 10.49% 92.71% ± 5.83% 99.99% ± 10.49% 82.88% ± 14.01% 92.71% ± 5.94% 14 days 93.44% ± 5.83% 61.20% ± 9.89% 93.44% ± 5.83% 61.20% ± 9.89% 93.51% ± 15.90%	Pvs Control Pvs Control Pvs Control Pvs Control Pvs Control	Pvs MDMA #### ##### Pvs MDMA #### ###### Pvs MDMA ################################	Pvs AMI+MDMA ns Pvs AMI+MDMA a Pvs AMI+MDMA 	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20% 85.29% ± 7.12% 21 days 105.23% ± 7.21% 68.53% ± 7.21%	Pvs Control	Pvs MDMA ### ## Pvs MDMA ### ## Pvs MDMA ### ##	Pvs AMIHMDMA Pvs AMIHMDMA Pvs AMIHMDMA Pvs AMIHMDMA	28 days 103.11% ± 10.8% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 93.31% ± 11.85% 75.46% ± 9.03% 91.70% ± 10.92% 28 days 101.57% ± 2.68% 68.15% ± 8.54% 83.64% ± 6.31%	Pvs Control ns Pvs Control Pvs Control Pvs Control ns	Pvs MDMA #### Pvs MDMA # # Pvs MDMA #	AVS AMHHMDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44% 90.96% ± 15.47% 98.60% ± 5.10% 35 days 93.53% ± 6.29% 83.47% ± 3.34% 91.55% ± 9.77%	Pvs Control ns ns ns Pvs Control Pvs Control Pvs Control ns ns ns	Pvs MDMA P ns ns Pvs MDMA P ns ## Pvs MDMA P ns ms ms	vs AMIHMDMA ns vs AMIHMDMA ns vs AMIHMDMA vs AMIHMDMA
Group A B C D Group A B C D Group A C D	ampusAnteri Control MDMA AMI+MDMA AMI control MDMA AMI+MDMA AMI+MDMA Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA	Baseline 100.00% 100.00% 100.00% 100.00% Baseline 100.00% 100.00% Baseline 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 5.83% 99.9% ± 10.49% 82.88% ± 14.01% 92.71% ± 5.94% 93.44% ± 5.83% 61.20% ± 9.89% 93.44% ± 5.83% 61.20% ± 9.89% 95.11% ± 15.90% 96.28% ± 7.95%	Pvs Control ns Pvs Control Pvs Control S Pvs Control Pvs Control T ns ns ns ns ns	Pvs MDMA #### ##### Pvs MDMA #### ##### Pvs MDMA #### #####	Pvs AMI+MDMA	21 days 103.27% ± 2.05% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20% 87.25% ± 15.20% 21 days 105.23% ± 7.21% 68.53% ± 7.12% 88.05% ± 2.85%	Pus Control	Pvs MDMA ### ## Pvs MDMA ## ## ## Pvs MDMA ### ## ## ## ## ## ## ## ## ## ##	Pvs AMI+MDMA	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 75.46% ± 9.03% 91.70% ± 10.92% 28 days 101.57% ± 2.68% 68.15% ± 8.54% 83.64% ± 6.31% 92.39% ± 5.41%	Pvs Control Pvs Control Pvs Control Pvs Control Pvs Control R	Pvs MDMA #### Pvs MDMA # # ## Pvs MDMA # # ##	NS AMIHMDMA ns NS AMIHMDMA ns NS AMIHMDMA ns	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44% 90.96% ± 15.47% 93.53% ± 6.29% 83.47% ± 3.34% 91.55% ± 0.77% 98.09% ± 5.35%	Pvs Control ns ns ns ns Pvs Control rs ns	Pvs MDMA P ns ns ns ns ns	vs AMI+MDMA ns vs AMI+MDMA ns vs AMI+MDMA ns
Group A B C D Group A B C D Group A B C D D D D	ampusAnteri Control MDMA AMI+MDMA AMI+ Control MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI+MDMA AMI	Baseline 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00% 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 97.52% ± 6.66% 97.82% ± 6.66% 14 days 99.28% ± 10.43% 99.71% ± 5.83% 92.71% ± 5.84% 92.71% ± 5.94% 14 days 93.44% ± 5.83% 61.20% ± 9.89% 89.51% ± 15.90% 96.28% ± 7.95%	Pvs Control 6 7 6 7 6 7 7 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 7 8 8 9	Pus MDMA	Pvs AMI+MDMA ns Pvs AMI+MDMA a Pvs AMI+MDMA ns	21 days 103.27% ± 2.05% 67.00% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 21 days 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20% 85.29% ± 7.12% 21 days 105.23% ± 7.21% 68.53% ± 7.21% 88.05% ± 12.88% 85.06% ± 8.65%	Pus Control	Pvs MDMA ### ### ### ### ### ### ### ### ### ### ###	Pvs AMI+MDMA ns Pvs AMI+MDMA ns Pvs AMI+MDMA ns ns	28 days 103.11% ± 10.8% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 59.31% ± 11.85% 91.70% ± 10.92% 28 days 101.57% ± 2.68% 68.15% ± 2.68% 68.15% ± 8.54% 83.64% ± 6.31% 92.39% ± 5.41%	Pvs Control Pvs Control Pvs Control Pvs Control R Pvs Control R R R R R R R R R R R R R	Pvs MDMA ### ### Pvs MDMA Pvs MDMA ## ##	2vs AMI+MDMA ns 2vs AMI+MDMA ns 2vs AMI+MDMA ns	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 8.35% 94.31% ± 7.44% 90.96% ± 15.47% 98.60% ± 5.10% 35 days 93.53% ± 6.29% 83.47% ± 3.34% 91.55% ± 9.77% 98.09% ± 5.35%	Pvs Control	Pvs MDMA P ns ns Pvs MDMA P ns ## Pvs MDMA P ns ###	vs AMI+MDMA ns vs AMI+MDMA ns vs AMI+MDMA vs AMI+MDMA ns
Group A B C D Group A B C D Group Group	impusAnteri Control MDMA AMI+MDMA AMI Control MDMA AMI+MDMA AMI Control MDMA AMI Control MDMA AMI+MDMA AMI Thalamus	Baseline 100.00%	14 days 105.12% ± 1.72% 65.29% ± 9.69% 92.28% ± 11.78% 97.52% ± 6.66% 14 days 94.28% ± 5.83% 59.99% ± 10.49% 92.71% ± 5.83% 61.20% ± 9.89% 93.44% ± 5.83% 61.20% ± 9.89% 95.51% ± 15.90% 96.28% ± 7.95% 14 days	Pvs Control Second Second Sec	Pvs MDMA	Pvs AMI+MDMA	21 days 103.27% ± 2.06% 67.00% ± 10.10% 88.45% ± 10.10% 88.45% ± 11.88% 92.78% ± 13.85% 105.23% ± 7.21% 64.28% ± 12.75% 87.25% ± 15.20% 85.29% ± 7.12% 05.23% ± 7.21% 68.53% ± 7.21% 68.53% ± 12.88% 85.06% ± 8.65% 21 days	Pvs Control	Pvs MDMA ### ## ### ## ### ## ### ##	Pvs AMI+MDMA	28 days 103.11% ± 10.89% 71.04% ± 5.22% 85.28% ± 9.06% 92.38% ± 10.02% 28 days 101.57% ± 4.43% 75.46% ± 9.03% 91.70% ± 10.82% 91.70% ± 2.68% 68.15% ± 2.68% 68.15% ± 5.41% 92.39% ± 5.41% 28 days	Pvs Control	Pvs MDMA #### # ### # ### # ### # ### # ### # ### # ### # ### # ### # ### # ### ## ##	2vs AMI+MDMA ns 2vs AMI+MDMA ns 2vs AMI+MDMA ns 2vs AMI+MDMA	35 days 105.84% ± 25.95% 87.69% ± 5.15% 97.55% ± 14.78% 95.89% ± 12.26% 35 days 98.78% ± 7.44% 90.96% ± 15.47% 98.60% ± 5.10% 35 days 93.53% ± 6.29% 83.47% ± 3.34% 91.55% ± 9.77% 98.09% ± 5.35% 35 days	Pvs Control ms Pvs Control ms ms Pvs Control Pvs Control Pvs Control Pvs Control Pvs Control	Pvs MDMA P ns Pvs MDMA P ns ## Pvs MDMA P ns ## Pvs MDMA P	vs AMIHMDMA ns ns vs AMIHMDMA ns vs AMIHMDMA vs AMIHMDMA
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Figure 6. Recovery in brain SERT availability in 9 brain areas under different drug treatment from day 0 to day 35. Data are mean \pm SD. Animals were grouped into (1) Group A: saline control; (2) Group B: MDMA; (3) Group C: AMI with MDMA; or (4) Group D: AMI alone. Different superscript symbols denote different level of significance (red * p < 0.05, ** p < 0.01, *** p < 0.005 Group B or C or D vs. Group A; blue # p < 0.05, ### p < 0.005, #### p < 0.001 Group A or C or D vs. Group B; a p < 0.05, Group A or B or D vs. Group C, ns = not significant).

2.2. Amitriptyline Accelerates SERT Recovery after MDMA Induction

In all brain regions, co-administration of AMI with MDMA resulted in higher 4-[¹⁸F]-ADAM uptake compared to the MDMA group (Figure 2). At day 14, the recovery rates of seven of the ten regions were significantly different between the two groups (MDMA vs. AMI + MDMA, blue # p < 0.05~### p < 0.001, Figures 5 and 6). AMI dramatically increased 4-[¹⁸F]-ADAM uptake in all brain regions (Figure 3 blue line), which enhanced the average ~18% recovery rate at day 14 when compared with the MDMA group (MDMA 71.29% ± 3.21% vs. MDMA + AMI 89.06% ± 3.38%; Figure 5 red vs. blue line). Thus, the effect of MDMA-induction or self-recovery rate varied in different regions. It seemed that AMI globally accelerated the SERT recovery rate from day 14 and then reached 96.23% ± 11.98% at day 35. Detailed results are summarized in Figures 4 and 6.

2.3. Amitriptyline Does Not Affect the Normal Brain

Since AMI was a non-selective SERT inhibitor, we further tested whether it altered normal brain SERT levels. The results showed that pre-treatment with AMI alone slightly decreased 4-[¹⁸F]-ADAM uptake in all brain regions. However, no significant effect is noted regarding the curves of SURs or recovery rate of the AMI group, showing a similar pattern with the controls (Figure 2A,B, Figures 3 and 5 green line). Detailed results are summarized in Figures 4 and 6.

3. Discussion

Using a selective SERT PET radiotracer, we monitored a long-term SERT occupancy/ recovery in vivo and evaluated the AMI neuroprotection after MDMA-induction. Our results showed that acute and repeated administration of MDMA significantly induced SERT reduction levels in all regions at day 14 compared to the controls, which was supported by previous studies, revealing that the effect of MDMA on SERT binding was a robust finding in rodents [4,10,43–45].

To quantify the long-term effects of MDMA exposure, we further investigated the effect of the duration of MDMA/ecstasy abstinence on SERT binding by examining the reversibility of SERT binding in vivo during a period of abstinence from MDMA. We found that neurotoxicity induced by MDMA in the rat brain was region-specific, reflecting the varied SURs or progression of the self-recovery rate of SERT. In the study period (35 days), we found the regions such as the thalamus, hypothalamus, hippocampus posterior, anterodorsal hippocampus and cingulate cortex (low-self-recovery rate) had relatively slower self-recovery progression compared to the motor cortex, striatum and auditory cortex, and visual cortex (mid- or high self-recovery rate). The results also indicated that the SERT self-recovery in the rat brain after MDMA-induction was time-dependent and returned to 90.90% \pm 7.63% of baseline values at day 35. The regions with low or mid-self-recovery rates in the present study were also previously found to be the regions most affected by MDMA [46,47].

Our findings agree with numerous previous studies that showed SERT loss in the cingulate cortex, hippocampus, entorhinal cortex, medial hypothalamic area, and the medial and lateral thalamic nuclei of rats, following MDMA administration in a rodent model [5,47,48]. Moreover, our results also demonstrated progressive self-recovery of SERT binding from 14 to 28 days following MDMA exposure, reaching >90% at day 35, in agreement with a previous rodent study [10,49]. Compared to rodents, in a primate study, Scheffel et al. (1998) showed that SERT binding increased from 40 days to 9 months after MDMA administration in the pons, midbrain, and hypothalamus. However, it decreased in cortical regions [50]. Ma et al. (2016) subsequently reported that the SERT recovery rate was an average of ~66.6% and ~68.6% after MDMA administration in the striatum, thalamus, and midbrain at 24 and 54 months, respectively [41]. In human studies, several reports demonstrated no difference in SERT binding between former ecstasy users and drug-naive controls after 1 year of abstinence [51–53]. Taken together, these neuroimaging studies

show reduced SERT levels are region-specific and SERT recovery positively correlates with the duration of MDMA abstinence.

Although efforts have been made to investigate the long-term effects of MDMA exposure, several questions remain. Firstly, what is the correlation between recovery of SERT binding and the function of SERT neurons? To address this concern, Li et al. (2010) reported that the density of serotonergic fibers and cell bodies was decreased at day 31 after MDMA treatment (10 mg/kg, i.p), when the SERT recovery rate was ~35.2% compared to the controls [10]. Andó et al. reported that 6 months after administering a high-dose (15 or 30 mg/kg, i.p), MDMA-induced damage of serotonergic axons showed recovery in most brain areas in rats [54]. Secondly, what is the correlation between recovery of SERT binding and cognitive impairments? In human study, several studies reported that after one year of abstinence, ex-MDMA users showed deficits in the Rey Auditory Verbal Learning Test, similar to current MDMA users, although SERT binding was similar to the control level [51]. A review of empirical research (2013) supported those cognitive impairments following MDMA administration, which could result in long-term cognitive effects, such as retrospective memory, prospective memory, higher cognition, problem-solving, and social intelligence. MDMA can also affect sleep architecture, sleep apnea, complex vision, pain, neurohormones, and psychiatric status [51].

Taken together, the evidence above indicates MDMA-induced reductions in SERT levels or serotonergic neurons across the cerebral cortex, associated with neurocognitive impairments. However, it is unclear whether the cause is associated with SERT neuron recovery or other causes. Future longitudinal studies are recommended to investigate the serotonin level in blood or cerebrospinal fluid [55] or behavior tests.

The present results demonstrate that co-administration of MDMA with AMI rapidly blocked MDMA-induced serotonin release and MDMA neurotoxicity and globally restored and largely accelerated SERT levels from day 14. Among all regions, those regions with low or mid-self-recovery rates had weaker responses to AMI when compared to regions with high recovery rates.

Li et al. (2010) reported that co-administration of MDMA with the SSRI fluoxetine restored SERT binding rate to ~79.6% of the control level at day 31 post-MDMA [10]. Compared to fluoxetine in the current results, AMI showed an 84.91% \pm 3.05% of recovery rate at day 28. AMI led to the largest (~18% higher) recovery rate compared to the MDMA group at day 14, then the differences narrowed as the MDMA group exhibited progressive self-recovery; the average recovery rate of MDMA with AMI group was ~12% higher compared to that of MDMA group from day 14 to 35. In other words, in general, it would take 35 days for the MDMA group to return to 90% of baseline SERT recovery, whereas AMI reduced this duration to only 14 days. The results could be explained by the higher neuroprotective effects of AMI through anti-apoptotic effects to prevent cell death caused by hydrogen peroxide (H₂O₂) and induction of subsequent oxidative stress mediated by MDMA [56].

Moreover, AMI was also reported to significantly improve long- and short-term memory and increase neurogenesis and neurosynaptic marker proteins in an AD mouse model [23]. Therefore, it would be interesting to further assess the AMI response using behavioral tests, as MDMA can have a long-term impact on cognitive impairment.

Another advantage of AMI, in contrast to the expensive, risk-overt, and time-consuming nature of de novo drug development, is that applying well-tolerated therapeutics in new pharmacogenomic settings may be a more effective approach. Seeking effective treatments based on Food and Drug Administration-approved drugs or so-called "drug repurposing" (i.e., using AMI for MDMA-induced serotonergic deficiency) has become a promising drug discovery route for neuroprotection in MDMA users.

Our immunochemical findings (Supplementary Materials) confirmed the PET study, revealing that at day 28 post-MDMA, the density of serotonergic fibers and cell bodies decreased in the MDMA group. On the contrary, co-administration of MDMA with AMI showed improvement in structural damage of serotonin neurons. The results were con-

sistent with several studies that reported dramatic decreases in SERT binding following various MDMA dosing regimens and post-administration [57]. This previous study also showed that the effect of MDMA on SERT depletion is region-specific. For example, areas such as the striatum and raphe nuclei seem to be affected more strongly than other areas such as the hypothalamus. In the long term, the evidence suggests that SERT gene expression is negatively regulated by MDMA exposure [58], leading to reductions in SERT binding and immunoreactive fiber density in the absence of physical damage.

Limitations

Only male rats were tested in this study; however, female rats have been reported to exhibit larger responses to the effects of MDMA, which could be explained by the effects of estrogen [59,60]. Thus, it would be interesting to investigate whether there are gender differences in the response to AMI. Also, further studies such as behavior tests (i.e., the sucrose preference test as a measure of anhedonia) could be employed post-MDMA to more fully integrate the PET results. Moreover, in the present study, we only used one dose of AMI to test our hypothesis; in vivo dose-dependent curves for AMI should be plotted in future research. Although we performed immunohistochemistry at day 28 to confirm the PET images, which was the optimal time-point to highlight the differences in SERT neurons among groups, the lack of IHC results for day 35 may be a minor drawback of the study, even though no significant differences were observed in the PET data at this timepoint.

4. Materials and Methods

4.1. Animals

All experimental procedures were performed in compliance with the Institutional Animal Care and Use Committee guidelines at the National Defense Medical Center, Taipei, Taiwan, R.O.C. (IAUIC number 10-093). Adult male Sprague–Dawley (SD) rats (250–300 g in weight) were housed at the National Defense Medical Center (Taipei, Taiwan) in animal facilities and maintained under light/dark cycle (from 7:00 AM to 7:00 PM) with a constant temperature of 23 ± 2 °C. Female rats were not used in this longitudinal study to avoid the influence of hormonal effects related to menstruation.

4.2. Drug Treatments and Study Design

MDMA (purity, 98%) was obtained from the Investigation Bureau of Taiwan, and AMI was purchased from Sigma-Aldrich (St. Louis, MO, USA). MDMA and AMI were dissolved in saline (0.9% NaCl) at a final concentration of 10 and 5 mg/mL, respectively.

To extend our previous studies on the effects of MDMA in rodents [41,61,62] and primates [4], we conducted the following study. A total of 24 rats were subjected to baseline (pre-drug) 4-[¹⁸F]-ADAM PET scans before any drug treatment. A week after the baseline PET scans, the same 24 rats were randomly assigned to (1) the normal control group (saline injection, n = 6), (2) MDMA group (10 mg/kg MDMA injection alone, n = 6), (3) AMI with MDMA group (5 mg/kg AMI followed by 10 mg/kg MDMA injection, n = 6), or the (4) AMI group (5 mg/kg AMI alone, n = 6). All drugs (or saline) were administered twice per day for four successive days (Day 1 to Day 4).

The experiment was conducted using 4-[¹⁸F]-ADAM PET imaging to measure SERT occupancy by MDMA and amitriptyline, as a method to gauge in vivo SERT binding of MDMA and AMI. Post-drug 4-[¹⁸F]-ADAM PET scans were performed weekly from day 14 to day 35 to measure SERT occupancy/recovery longitudinally. At day 28, three rats in each group were euthanized for immunohistochemistry; the remainder of the rats were subjected to 4-[¹⁸F]-ADAM PET imaging on day 35. The experimental design is schematically illustrated in Figure 7.



Figure 7. Schematic and graphical representation of the study design. A total of 24 rats underwent 4-[¹⁸F]-ADAM PET imaging at baseline (pre-drug). One week later, animals were randomly grouped into 4: Group 1 as a control, Group 2 MDMA alone, Group 3 AMI with MDMA, Group 4 AMI alone. Rats received drug treatment twice daily on days 1, 2, 3, 4. Then, 4-[¹⁸F]-ADAM micro-PET imaging was performed on days 14, 21, 28, and 35. Immunohistochemistry was performed on day 30 (n = 3/group, Supplementary Materials) and the rest of animals were used for the end point imaging on day 35.

4.3. Radiopharmaceutical

Moreover, 4-[¹⁸F]-ADAM was synthesized in an automated synthesizer as described previously. Briefly, nucleophilic fluorination of N,N-dimethyl-2-(2,4-dinitroph-enylthio) benzylamine in dimethyl sulfoxide with dried potassium [¹⁸F]fluoride/ Kryptofix 2.2.2 at 120 °C is reduced with Cu(OAc)2-NaBH4 in EtOH at 78 °C. Purification with high-performance liquid chromatography (HPLC) produced the desired compound with a radiochemical yield (EOS) of ~3%, in a synthesis period of 120 min. The radiochemical yield of 4-[¹⁸F]-ADAM increased to ~15% when using a different precursor and synthesized manually [38]. The chemical and radiochemical purities were > 95%, and the specific activity was >3 Ci/µmol (111 GBq/µmol).

4.4. Image Data Acquisition and Analyses

Imaging was performed according to a previous report [37] with minor modifications. Rats were anesthetized by passive inhalation of isoflurane/oxygen mixture (5% isoflurane for induction and 1% for maintenance). After 60 min of administration of 4-[¹⁸F]-ADAM (14.8–18.5 MBq; 0.4–0.5 mCi) via tail vein, the static PET images were acquired for 30 min using a Concorde R4 Microsystem (Knoxville, TN, USA), which produced 63 image slices over a 7.89-cm axial field of view, with a slice thickness of approximately 1.25 mm. All images were reconstructed with the Ordered Subset Expectation Maximum (OSEM) algorithm, producing a 128×128 -pixel image matrix, 16 subsets, four iterations, and a Gaussian filter. Then, images were reconstructed by the Fourier rebinning algorithm and two-dimensional filtered back-projection, applying a ramp filter cutoff using the Nyquist frequency. The reconstructed images were analyzed with PMOD (PMOD Technologies, Zürich, Switzerland) to measure standardized uptake value (SUV) in various brain regions. Volumes of interest of the striatum, auditory cortex, cingulate cortex, visual cortex, anterodorsal hippocampus, hippocampus posterior, hypothalamus, thalamus, and cerebellum were drawn manually on the reconstructed PET images, using an MRI-based rat brain atlas with PMOD (PMOD Technologies, Switzerland). The regional radioactivity concentrations (KBq/mL) of 4-[¹⁸F]-ADAM PET were estimated from the maximum pixel values within each ROI and expressed as SUV.

The final data were expressed as specific uptake ratios (SURs), expressed as (SUV_{target region} – SUV_{cerebellum})/SUVcerebellum. The SERT recovery rate was calculated as (SUR_{post-drug} – SUV_{baseline}) × 100%.

4.5. Statistical Analysis

Specific uptake rate differences of the two groups were compared using one-way analysis of variance (One-way ANOVA) and post hoc Bonferroni adjustment. P-values less than 0.05 (*), or less than 0.01 (**) or less than 0.005 (***) or less than 0.0001 (****) indicate significant difference. Data expressed as mean \pm standard deviation (mean \pm SD). Statistical analyses were performed using GraphPad Prism 8 (GraphPad software, La Jolla, CA, USA).

5. Conclusions

Based on the longitudinal in vivo 4-[¹⁸F]-ADAM PET, the present study found a clear loss of SERT binding sites in rats after the low-dose MDMA regime. We demonstrated that SERT recovery was positively correlated to the MDMA-abstinence duration, implying that the lower SERT densities in MDMA-induced rats reflected neurotoxic effects, which varied by region and were reversible. Current data also supported that AMI might have neuroprotective effects that globally accelerate the recovery rate of SERT, besides its antidepressive effects. Future studies should verify the neuroprotective effects of AMI in neuronal cells.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijms23137035/s1.

Author Contributions: Conceptualization, K.-H.M. and W.-S.H.; formal analysis, S.H.-H.Y. and T.-H.Y.; investigation, C.-J.T., C.-H.C. and Y.-Y.K.; data curation, Y.-Y.K. and L.G.F.II; writing—original draft preparation, S.H.-H.Y.; writing—review and editing, S.H.-H.Y. and W.-S.H.; funding acquisition, K.-H.M. and W.-S.H. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Ministry of Science and Technology R.O.C. (MOST-109-2314-B-038-151, MOST-110-2314-B-A49A-528, 109-2314-B-016-014-MY2), Development Center for Biotechnology (110M0156) and The Featured Areas Research Center Program within the framework of the Higher Education Sprout Project by the Ministry of Education (MOE) in Taiwan.

Institutional Review Board Statement: The animal study protocol was approved by the Institutional Animal Care and Use Committee guidelines at the National Defense Medical Center, Taipei, Taiwan, R.O.C. (IAUIC number 10-093).

Informed Consent Statement: Not applicable.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article.

Acknowledgments: A preprint has previously been published at Pre-print [63]. We thank the Molecular Imaging Facility Small Animal 7T PET/MR and Brain Research Center at National Yang Ming Chaio Tung University for technical support.

Conflicts of Interest: The authors declare no conflict of interest.

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