SUPPLEMENTARY MATERIAL

During the 1970s and early 1980s, studies of the mechanism of psychostimulant drugs focused on two questions: 1. determining whether psychostimulant action was mediated primarily by dopamine or norepinephrine, and 2. in the case of dopamine, determining the relative contribution of the mesoaccumbens and nigrostriatal pathway. A variety of strategies were employed, including different lesion methods and different targets, such as lesioning the dopamine nuclei, projection areas, or fibers of passage. When confronted with contradictory results, the variety of methods made it difficult to compare findings and resolve discrepancies. Nonetheless, it became evident that controlling the scope of the lesion so that it was, on one hand, sufficiently complete to achieve measurable behavioral effects while, on the other hand, sufficiently localized so as to not cause confounding collateral damage, was problematic. On the whole, these studies consistently demonstrated that the dorsal striatum was the critical substrate mediating psychostimulant induced stereotypy. The majority (though not all) of the studies found the nucleus accumbens to be critically involved in psychostimulant induced locomotor activity. Determining the role of the nigrostriatal pathway in the acute locomotor response, however, remained inconclusive. To our knowledge, a compelling demonstration of the role of the nigrostriatal pathway in mediating the acute locomotor response to psychostimulants is still lacking. In the supplementary table, we provide a partial list of studies that attempted to resolve this question and their findings.

Report	Year	Lesion Method	Findings	DSt Required?	Comments
Naylor and Olley	1972	Electrolytic lesion of caudate-putamen or globus pallidus	No change in locomotor response to AMPH in lesioned rats	NO	
Creese and Iversen	1972	6-OHDA injection into substantia nigra	85-90% striatal DA depletion not sufficient to abolish AMPH locomotor response	NO	Abolished stereotypy response but not locomotor response to AMPH
Creese and Iversen	1973	Intraventricular 6-OHDA injection at 5,7 or 9 days postnatally	Report 98% destruction of striatal DA terminals and loss of AMPH locomotor response	YES	Do not discriminate dorsal/ventral striatum; confounding destruction of noradrenergic system
Fibiger et al	1973	6-OHDA either intraventricularly or into substantia nigra	Reduced AMPH locomotor response	YES	Intraventricular and SN administration showed same effect
Costall and Naylor	1973	Electrolytic lesion of substantia nigra	No reduction in locomotor response to AMPH	NO	Not specific to DA cells; effect of lesion dependent upon strain and activity levels prior to lesion
Neill et al	1974	Electrolytic lesions of dorsal or ventral striatum	Neither altered AMPH Locomotor response	NO	Neither dorsal or ventral lesion altered locomotor response to AMPH; ventral lesion may have damaged nigrostriatal pathway
Iversen et al	1975	6-OHDA lesions of either caudate or nucleus accumbens	Caudate, no effect; NAc, diminished locomotor response	NO	Caudate DA reduced by only 50%; Caudate lesion reduced stereotypy response

Roberts et al	1975	6-OHDA lesion of substantia nigra (injection into zona incerta region)	Report 92% depletion of dorsal striatal DA and severely reduced locomotor response to AMPH	YES	May have lesioned part of ventral system as well.
Brook and Iversen	1975	6-OHDA lesion of substantia nigra	Reprot 80-90% loss of striatal DA; No reduction of locomotor response to AMPH in lesioned rats	NO	Discussion of time-course of changes following lesions
Kelly et al	1975	6-OHDA lesions of either caudate or nucleus accumbens	NAc lesions decreased AMPH locomotor response; DSt lesions did not	NO	Only 51% depletion of striatal DA; Accumbens lesion resulted in 79% DA depletion and 89% noradrenaline depletion
Creese and Iversen	1975	6-OHDA lesion of substantia nigra	Abolished locomotor response to AMPH and cocaine	YES	Lesions may have damaged mesoaccumbens fibers as well.
Pijnenburg et al	1975	Injected haloperidol into the caudate and nucleus accumbens	haloperidol in NAc diminished locomotor response to AMPH; haloperidol in caudate did not	NO	Injection in caudate may not have been extensive enough to observe behavioral alterations
Costall et al	1977	6-OHDA lesions of several areas, including central caudate, anterior caudate, nucleus accumbens and substantia nigra.	Neither the NAc or caudate lesions reduced locomotor response to AMPH; SN lesion increased response.	NO (NAc no effect either)	Provides a good summary of literature to date

Fink and Smith	1979	6-OHDA lesions of anterior caudate or nucleus accumbens	No effect of dorsal or ventral lesion in total activity response to AMPH	NO (NAc no effect either)	1. No lesion of dorsal-lateral 2. in an unusual measure of complete traversals across the chamber rather than total activity, the DSt lesion caused a reduction.
Fink and Smith	1980	Series of 6-OHDA lesions in different regions of striatum, ranging from exclusively accumbens to exclusively dorsomedial striatum	Both the dorsomedial and nucleus accumbens lesion resulted in only 20% diminution of locomotor response to AMPH	As important as NAc	Concludes that specific region does not mediate locomotor response but that response is broadly distributed across striatum
Jones and Robbins	1992	6-OHDA lesions of nucleus accumbens, caudate and prefrontal cortex	caudate lesion did not alter locomotor response	NO	1. In caudate lesion, DA reduced by 43% in anterior region and 76% in posterior region, lesion may not be sufficiently complete to observe effect. 2. Accumbens lesion depleted dopamine in anterior caudate to greater extent than caudate lesion

Supplementary Table. Review of lesion studies examining role of dorsal striatum in locomotor response to psychostimulants. Abbreviations: AMPH, amphetamine; NAc, nucleus accumbens; SN, substantia nigra; DSt, dorsal striatum; 6-OHDA, 6 hydroxy dopamine; DA, dopamine.

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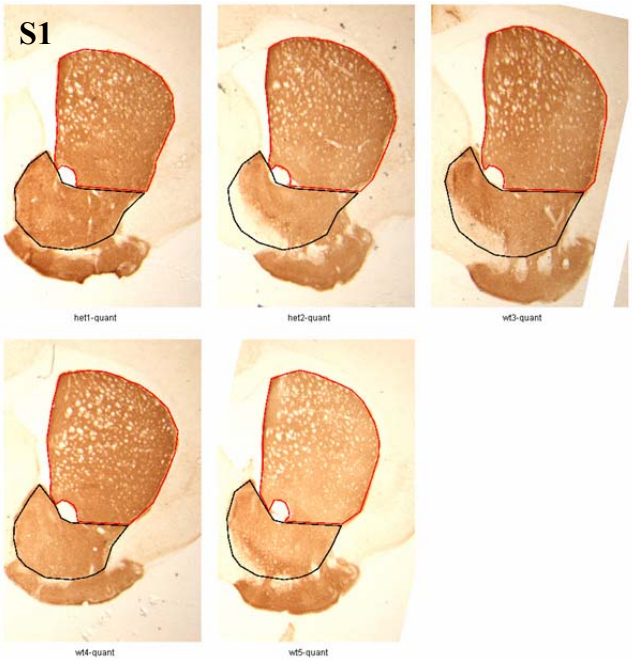

Figure S1 Sections and drawn regions of interest used to quantify TH reactivity in heterozygote and WT mice.

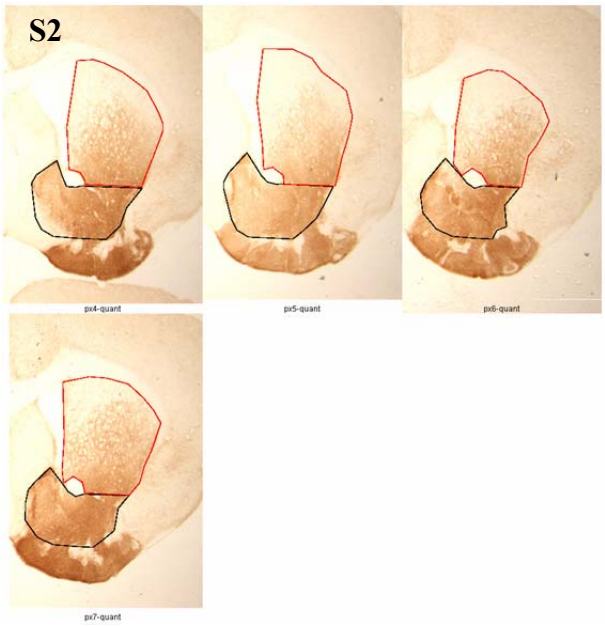

Figure S2 Sections and drawn regions of interest used to quantify TH reactivity in Pitx3-deficient mice older than 100 days.

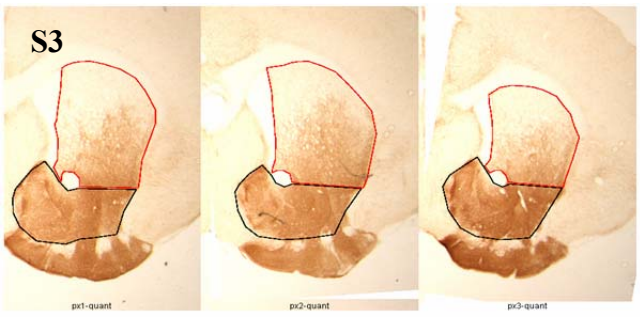

Figure S13 Sections and drawn regions of interest used to quantify TH reactivity in Pitx3-deficient mice younger than 100 days.

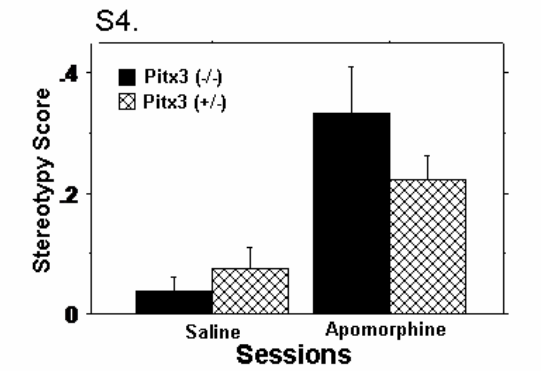

Figure S4. Stereotypy in response to apomorphine challenge. Mice were challenged with saline (left bars) and apomorphine (2 mg/kg, right bars) in two open field sessions on consecutive days. The sessions were recorded and stereotypy was visually scored as described in methods.