Published in final edited form as:

Biol Psychiatry. 2016 June 01; 79(11): 872–874. doi:10.1016/j.biopsych.2016.04.013.

A NAc for Spinal Adjustments After Cocaine or Stress

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A central structure in the mammalian neuronal “reward” pathway is the nucleus accumbens (NAc), particularly its more medial shell (NAcSh) component. Motivation for both natural and pathologically linked rewards, such as drugs of abuse, is driven by the convergence of cortical and subcortical glutamatergic input and ventral midbrain dopaminergic input onto the head and neck, respectively, of the dendritic spines of NAcSh gamma-aminobutyric acidergic medium spiny neurons (MSNs) (1–3). Many studies on NAcSh MSNs and neurons in other brain regions suggest that experience-dependent changes in spines—their number, density, or morphology (e.g., thin/immature vs. mushroom/mature)—are linked to behavior (4). Such experience-dependent “spinal adjustments” are often discussed as correlates and even as causal factors of behavior alongside other prominent neuroadaptations, such as synaptic strength, a relativistic measure of synaptic transmission that is often indicated by the ratio between responses to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and *N*-methyl-D-aspartate receptors (1).

Changes in spines and synaptic strength are not the only factors driving behavior. For example, manipulations that can increase NAc MSN spines and alter synaptic strength, such as extended administration of cocaine or repeated stressful experiences (2,5), can often result in distinct behavioral outcomes. This leads to three of the questions asked in an article in this issue of *Biological Psychiatry* (6). First, could there be a specific postsynaptic explanation as to why both cocaine and stress can increase spine number and synaptic strength but diverge in their behavioral output? Second, do synaptic and spine dynamics differ in NAc output via subpopulations of MSNs expressing dopamine D₁ receptors (D1-MSNs), which directly innervate the ventral midbrain, and D2-MSNs, which indirectly innervate the midbrain via the globus pallidus (Figure 1)? Third, can data that cocaine and stress tend to increase spine number and density be reconciled with the lack of agreement on whether, where, and how cocaine and stress change synaptic strength (1,3,5)? As the major output neurons of the NAc and thus key neural arbiters of the reward pathway, clarification of synaptic and spine changes in gamma-aminobutyric acidergic D1-MSNs and D2-MSNs in basal and pathologic conditions (e.g., stress and drug addiction) is fundamental to comprehending the neural basis of motivated behaviors.

The article by Khibnik *et al.* (6) is not the first publication to broadly address such questions. However, there are several aspects that make their work stand out. Given the intricacies of

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Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

such experiments—with variables of brain region (NAc core vs. NAc shell), MSN subpopulation (D1-MSN vs. D2-MSN), stimuli (cocaine vs. stress), and even spine type (e.g., thin vs. mushroom)—it is typical for researchers to focus on just one set of comparisons. The study by Khibnik *et al.* is notable for its investigation of several of these variables; the authors examine MSN subpopulations (using a well-verified D2-MSN reporter mouse line), stimuli known to increase NAc spine number (repeated cocaine vs. social defeat stress), and two spine types (thin and mushroom). Also, studies of synaptic strength after cocaine or stress typically stimulate presynaptic terminals to assess synaptic strength and then experimentally tease apart the influence of both presynaptic (e.g., calcium influx, neurotransmitter release probability, autoreceptor expression) and postsynaptic (e.g., spine number, receptor composition) factors. Khibnik *et al.* remove the variation that can accompany presynaptic terminal stimulation by instead using two-photon glutamate uncaging along with ex vivo spine imaging to answer the question of how cocaine versus stress influences synaptic strength of NAcSh of D1-MSNs versus D2-MSNs (Table 1).

Using their single spine manipulation, Khibnik *et al.* (6) found that NAcSh D1-MSN spines had smaller synaptic responses a short time after either repeated cocaine or social defeat stress relative to respective control animals. These observations were consistent across the entire measured spine population (cumulative frequency) for both cocaine and stress. This suggests that although cocaine and stress both tend to increase spine number or density, they ultimately lead to contrasting functional alterations, which are associated with a redistribution of synaptic strength across a population of D1-MSN spines. These opposing changes in synaptic strength after cocaine versus stress mirror some, but not all, of the psychotropic or stress-induced changes in presynaptic terminal stimulation (7,8) or more indirect synaptic or static measures of the postsynaptic surface (9). Moving forward, it can be hypothesized that this contrasting redistribution of synaptic strength on D1-MSNs after cocaine or stress is a defining characteristic underlying behavioral differences, an idea recently touched on in another paper using the same chronic social defeat stress paradigm (10).

Prior work also suggested that cocaine-induced synaptic adaptations and related spinal adjustments generally occur at D1-MSNs but not at D2-MSNs. However, Khibnik *et al.* (6) showed that cocaine induced a rightward shift in cumulative frequency in D2-MSN spines. Redistribution in synaptic weights was also evident after social defeat stress. In resilient/unsusceptible mice (“nondepressed” animals who approach rather than avoid an aggressor after repeated defeat bouts), NAcSh D1-MSN spines had greater synaptic responses relative to control mice, whereas D2-MSN spines had smaller synaptic responses. In susceptible mice (“depressed” animals who avoid rather than approach an aggressor), NAcSh D1-MSN spine synaptic strength was similar to control mice, but D2-MSN spines had decreased synaptic strength relative to control mice, on par with the decrease seen in resilient mice. Khibnik *et al.* were likely able to measure such D2-MSN synaptic strength changes because of their stimulation of a single spine. Although the authors suggest that their result is consistent with recent work on stress (10) in which activation of D2-MSNs led to susceptibility and activation of D1-MSNs led to resilience, the parallel is not precise, as an interpretation of the data of Khibnik *et al.* is that both susceptible and resilient effects have decreased synaptic strength at D2-MSNs, with the resilient effect just being greater.

Another notable set of findings from Khibnik *et al.* (6) is that a similar proportion of thin spines was responsive versus unresponsive to glutamate across experimental groups and that only mushroom, not thin, spines displayed altered synaptic strength after cocaine or stress. These findings add to the literature that mushroom spines—whose larger postsynaptic density and size are thought to correlate to the amount of canonical, synaptic AMPA receptors—respond to glutamate and are adaptive in the face of stimuli. However, another interpretation is that thin spines do respond to glutamate, in contrast to published data that they are “silent synapses,” hosting *N*-methyl-D-aspartate but not canonical membrane AMPA receptors (4). One hypothesis emerging from these mushroom versus thin spine findings is that the balance of mushroom versus thin spines on individual NAcSh MSNs may change over time, that these putatively newly formed thin spines contribute to alterations in synaptic transmission, and that they trigger adaptations in synaptic strength seen in mushroom spines (2).

A tempting conclusion from these results is that synaptic efficacy is divergently influenced by cocaine versus stress and in D1-MSNs versus D2-MSNs. The authors themselves are careful to point out the caveats in making such conclusions, given that published results vary based on species used, paradigm of stimuli exposure/drug administration, approaches to visualize spine dynamics or estimate synaptic strength, and length of time drug or stress free. The importance of these caveats are exemplified by data that withdrawal from cocaine (3 or 10 days) or morphine (2 weeks) can increase or decrease synaptic strength at D1-MSNs or D2-MSNs, respectively (2,7,8).

Several questions emerge from this work. What are the stability and persistence of the changes reported by Khibnik *et al.*? Do these changes modify dendritic integration of subsequent stimulations? What are the biochemical or molecular mechanisms underlying the cell type–specific spinal adjustments reported here (4)? Are they distinct for the NAcSh versus other brain regions or among different experiences (7)? From a local circuit level, is there a compensatory shift between cell types and spine types? What role does input specificity or long-range circuit specificity play in these changes (9)? Finally, how do these changes relate to persistence of drug- and stress-related behavior, and are there general principles that emerge that allow us to influence such behavior? It remains unclear whether spines are at the epicenter of behavior, are epiphenomena, or are somewhere in between. However, given the technical arsenal used in the study by Khibnik *et al.* and other technologies to more accurately follow and manipulate spines and behavior, researchers are poised in the next decade to make notable progress in “cracking” the code of how neuronal spinal adjustments relate to complex and motivated behaviors.

Acknowledgments

This work was supported by the National Institutes of Health Grant Nos. DA023555, DA023555, and MH107945 (to AJE), Brain and Behavior Research Foundation NARSAD Young Investigator Award (to SK), and National Aeronautics and Space Administration Grant No. NNX15AE09G (to AJE). MLM and EMA are supported by the National Institutes of Health Institutional T32 Grant No. DA007290 (PI AJE).

We thank Craig Powell for helpful discussions.

Effective September 1, 2016, Dr. Eisch is an employee of the University of Pennsylvania Perelman School of Medicine and the Children’s Hospital of Philadelphia.

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Figure 1.

Schematic of glutamate uncaging at a single mushroom spine of a D₂ receptor-expressing medium spiny neuron (D₂-MSN) in the nucleus accumbens shell, as applied in Khibnik *et al.* (6). D₂-MSNs (green) and D₁ receptor-expressing MSNs were examined in *Drd2*-EGFP transgenic mice. Key output structures of D₂-MSNs and D₁-MSNs are indicated to highlight their involvement in the indirect vs. direct pathway from the nucleus accumbens shell to the globus pallidus and ventral tegmental area (VTA). The box on D₂-MSN represents a secondary dendritic branch region analyzed by Khibnik *et al.* (6). A portion of the box is magnified (right) to depict a mushroom and thin spine on a D₂-MSN as well as photo conversion of glutamate and its action at synaptic and extrasynaptic sites. Alexa Fluor 594 used in Khibnik *et al.* (6) in D₂-positive MSNs not shown. Images not drawn to scale. AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; EGFP, enhanced green fluorescent protein; NMDAR, *N*-methyl-D-aspartate receptor.

Table 1

Overview of Cell Type–Specific Changes in Synaptic Strength at Mushroom Spines in Nucleus Accumbens Shell Medium Spiny Neurons, as Reported by Khibnik *et al.* (6)

	D1-MSN	D2-MSN
Cocaine	↓	↑*
Stress		
Susceptible	Ø	↓* ^a
Resilient	↑	↓*

Cocaine- and stress-induced changes were reported compared respective control animals (6). Table results are from glutamate photo-uncaging experiments performed at mushroom spines; stimulation of thin spines did not change measures of synaptic strength. For the purposes of this table, changes in unitary excitatory postsynaptic current amplitude or shifts in cumulative frequency are considered as changes in synaptic strength.

D1-MSN, D1 receptor–expressing medium spiny neuron; D2-MSN, D2 receptor–expressing medium spiny neuron; ↓, decreased synaptic strength; ↑, increased synaptic strength; ↓*, left-shifted cumulative frequency; ↑*, right-shifted cumulative frequency; Ø, no change detected.

^aIncrease/upward shift in frequency of certain amplitude unitary excitatory postsynaptic currents only in susceptible mice, as suggested by Khibnik *et al.* (6).