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Commentary: Methamphetamine abuse impairs motor cortical plasticity and function

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A commentary on

Methamphetamine abuse impairs motor cortical plasticity and function
by Huang, X., Chen, Y.Y., Shen, Y., Cao, X., Li, A., Liu, Q., et al. (2017). Mol. Psychiatry 22, 1274–1281. doi: 10.1038/mp.2017.143

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Psychiatric diseases demonstrate plasticity deficits in the brain. Animal studies have investigated the topic extensively. For instance, brain slice experiments with hippocampus/cortex preparations revealed plasticity changes in synaptic transmission of certain pathways, in a line with the learning and memory impairments in certain psychiatric diseases (Duman et al., 2016). Addiction is associated with synaptic transmission changes in mesolimbic and mesocortical pathways, with alterations of synaptic plasticity reported (Lüscher and Malenka, 2011). With an arsenal of animal reports on addiction evoked brain plasticity, surprisingly there were few studies translating such findings onto human subjects (Etkin, 2016). In a recent study published on the journal of *Molecular Psychiatry*, Huang et al. heroically investigated the cortical functional changes following methamphetamine abuse both in animal model and human addicts (Huang et al., 2017).

The authors firstly set up the animal model of methamphetamine self-administration and examined the synaptic plasticity on brain slices. The results showed that motor cortical, and dorsal-lateral rather than dorsal-medial striatal pathways exhibited impaired plasticity induction. Interestingly, molecular expression of GluN3A-containing NMDA receptors seems to be attributed for the altered plasticity. This is in a line with the previous finding that insertion of GluN3A-containing NMDA receptors at midbrain dopamine neurons resulted in anti-hebbian like plasticity (Mameli et al., 2011), given the fact that these NMDA receptors are less calcium permeable than canonical NMDA receptors.

To correlate the animal findings with human cortical plasticity, the authors employed a surrogate of synaptic plasticity in human—the plasticity of transcranial magnetic stimulation (TMS)-induced motor evoked potential (MEPs) (Huang et al., 2005), to dissect the potential impacts of methamphetamine on motor cortex. Notably, the Long-term potentiation (LTP) or Long-Term depression (LTD)-like changes of MEPs were both impaired in methamphetamine abusers, indicating that the cortical plasticity is impaired in human addicts. Interestingly, the plasticity deficits were in parallel with motor learning impairments, both in animal and human subjects (**Figure 1**).

Motor cortex is commonly a neglected region in addiction field. However, neuroimaging findings demonstrated that craving evoked by drug-associated cues involved motor and sensory regions (Yalachkov et al., 2010). In addition, animal studies detected drug cue-associated c-Fos expression in dorsal striatum (Willuhn and Steiner, 2006). Most importantly, the compulsive drug taking behavior could share certain neural pathways as obsessive compulsive disorder (OCD),

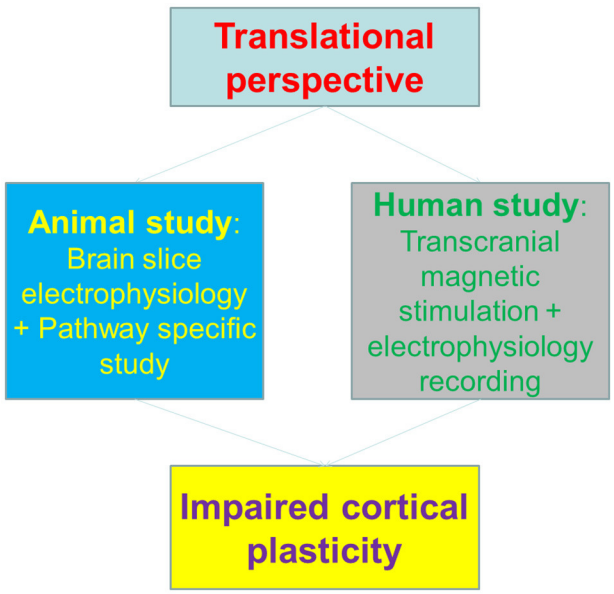

FIGURE 1 | The translational perspective and working scheme of Huang et al. paper.

therefore motor-striatal pathway might represent a new target in drug addiction (Everitt and Robbins, 2005). Indeed, exercise therapy is proved with efficacy in addiction rehabilitation, both in animal studies and human patients (Sanchez et al., 2015). Future studies are required to further elucidate if targeting motor cortex could bring benefits in addiction rehabilitation. Interesting, in addition to methamphetamine addiction, heroin addicts also exhibited cortical plasticity deficits (Shen et al., 2017).

Cortical plasticity is affected by a number of factors, such as genetic susceptibility to activity-dependent plasticity, trophic factor expression, neurotransmitters (Li Voti et al., 2011). Besides its applications on treatment of addiction or psychiatric diseases (Shen et al., 2016; Diana et al., 2017), TMS provides the unique chance to translate previous animal findings onto human subjects, the results of which could be taken for disease state diagnosis or prognosis for therapeutic treatments. In the future, TMS dependent measurements of EEG signals could provide functional cortex mapping non-invasively, but with much higher temporal resolution than brain imaging (e.g., fMRI; Miniussi and Thut, 2010). This will largely expand our understanding in addiction related brain functional changes, and to develop potential treatment against substance abuse.

Cortical plasticity impairment, however, is not limited to addiction. Previous studies reported that schizophrenia (Fitzgerald et al., 2004; Zhou et al., 2017), depression (Duman et al., 2016), and Alzheimer's disease (Di Lorenzo et al., 2016) patients also exhibited cortical function changes and plasticity deficits. This suggested that cortical functioning or ability of cortical modulation were blunted in these diseases. It is highly plausible that certain type of molecules (e.g., GluN3A) are involved in development and progression of these diseases (Pérez-Otaño et al., 2016); it is also possible that there are different factors altered in these diseases, though converged into the commonality of plasticity deficits. In addition, the circulating BDNF or neurotransmitter levels could be similar across different cortical areas, due to the diffusion with cerebrospinal fluid, resulting in changes of both motor cortex and other cortical areas simultaneously. These possibilities are worth of future investigation.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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