Evidence of Brain Damage in Chronic Ketamine Users
– a Brain Imaging Study

**Executive summary**

The objectives of this study were to ascertain the pattern of grey and white matter volume reduction and regional metabolic and activation abnormalities in chronic ketamine users, and to evaluate the correlations between these brain abnormalities and cognitive impairments in chronic ketamine users in Hong Kong.

One hundred and eighty-one participants were recruited from October 2011 to July 2015. The participants were divided into two groups: ketamine users (124) and healthy controls (57). Amongst the ketamine users, 60 were primarily ketamine users and 64 were poly ketamine users. Psychiatric assessments included self-rated questionnaires and face-to-face interviews. All participants completed a detailed cognitive battery that covered general intelligence, verbal and visual memory, executive functions, motor speed and language. All participants underwent magnetic resonance imaging scan of the brain.

Many participants in the ketamine users group also frequently used cocaine and cannabis. Among the ketamine users, 25% were diagnosed with a mood disorder and 15.3% with an anxiety disorder. The participants in the ketamine users groups, particularly in poly ketamine use group, had worse performance than the healthy controls on tests of general intelligence, verbal, visual and working memory and executive functioning.

In terms of grey matter volumes, the right orbitofrontal cortex, right medial prefrontal cortex, left globus pallidus, left hippocampus, and right nucleus accumbens
were smaller in the ketamine users group. In contrast, the volumes of the left caudate and left thalamus were higher in the ketamine users group. In terms of white matter volumes, the ketamine users group had a lower periventricular white matter volume in the right hemisphere. The grey matter volumes of the right orbitofrontal cortex, right medial prefrontal cortex, and right nucleus accumbens were negatively correlated with the severity of ketamine dependence. The right orbitofrontal cortex, right medial prefrontal cortex, left caudate, left globus pallidus, left hippocampus, right nucleus accumbens, left thalamus and right periventricular white matter were also correlated with the performance on the cognitive tests.

In terms of regional metabolism, there were no significant differences in the metabolite ratios between the primarily ketamine users group and the healthy control group; whereas the poly ketamine users group had a higher ‘glutamate + glutamine / creatine’ ratio in the right basal ganglia than the healthy control group.

A functional connectivity examination of the default mode network revealed significantly decreased connectivity in orbital part of inferior frontal gyrus, anterior cingulate and paracingulate gyri, superior temporal gyrus and vermic lobule VI; and increased connectivity in middle occipital gyrus in ketamine users.

In conclusion, the results provide imaging evidence of brain damage in chronic ketamine users. Chronic ketamine use was associated with reduced grey and white matter volumes in certain regions of the brain. Chronic ketamine use was also associated with altered functional connectivity with the default mode network. Abnormal brain structures and altered functional organisation of the brain network may underlie the hypersensitivity towards drug related cues but weakened cognitive control in those with ketamine
addiction. Longitudinal or prospective studies would help to strengthen the evidence on the reversibility of the structural and functional brain damage caused by ketamine.