

# **Evidence of Brain Damage in Chronic Ketamine Users**

## **– a Brain Imaging Study**

### *Executive summary*

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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.

# 長期使用氯胺酮對腦部的損害 — 腦部影像研究

## 行政撮要

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本研究的目的旨在 1.) 確定長期氯胺酮使用者灰質和白質容量減少與局部性代謝和激活異常的模式，2.) 評估長期氯胺酮使用者腦部上述結構性、代謝性和功能性異常與認知障礙的相關性。

自 2011 年 10 月至 2015 年 7 月，共 181 名受試者入組。受試者分為 2 組：氯胺酮組和健康對照組，氯胺酮組組有 124 名受試者，而健康對照組則有 57 名受試者。氯胺酮組中包括 60 名主要氯胺酮濫用者和 64 名氯胺酮及多種藥物濫用者。精神狀況評估包括問卷篩查和面談。所有受試者均完成一套詳細的認知測試。該測試涵蓋一般智慧、詞語記憶、視覺記憶、執行功能、動作速度和語言。每名受試者均會接受腦部磁力共振掃描檢查。

氯胺酮組受試者除氯胺酮外主要濫用可卡因和大麻。氯胺酮濫用者中，有 25% 患有抑鬱障礙，15.3% 患有焦慮症。兩組氯胺酮濫用組 (尤其氯胺酮及多種藥物濫用者) 與健康對照組在一般智慧、詞語記憶、視覺記憶、執行功能仍存在顯著差異，氯胺酮濫用組得分低於健康對照。

氯胺酮組右側眶額葉、右內側前額葉、左側蒼白球、左側海馬、右側伏隔核的灰質體積小於對照組，而左側尾狀核和左側丘腦的體積則大於對照組。此外，氯胺酮組右側腦室旁白質體積低於對照組。在氯胺酮組中，右側眶額葉、右內側前額葉、右側伏隔核灰質體積與氯胺酮成癮嚴重程度呈負相關關係。右側眶額葉、右內

側前額葉、左側尾狀核、左側蒼白球、左側海馬、右側伏隔核、左側丘腦和右側腦室旁白質與認知測試表現呈相關關係。

主要氯胺酮濫用組與對照組相比代謝物濃度沒有顯著差異，而氯胺酮及多種藥物濫用組在右側基底節的“谷氨酸+谷氨酰胺/肌酸”比高於對照組。氯胺酮組靜息態預設模式網路連接在前額眶內部分、前扣帶回和半扣帶回部分、顳上回和vermic 葉 VI 活性下降，而枕中回活性增強。

總括而言，氯胺酮濫用對大腦的損傷有影像學依據。氯胺酮濫用與特定腦區灰質和白質體積下降有關並且蝕變預設模式網路的功能連線性。異常的腦體積和腦神經網路的功能連接可能導致氯胺酮濫用者的認知功能改變，對濫藥相關線索的敏感性增強而對成癮行為的控制減弱。氯胺酮所致的這些大腦結構及功能變化是否可逆轉還需要縱向或前瞻性的研究來進一步證明。