Table DS1  Linear regression imaging outcome parameters

<table>
<thead>
<tr>
<th>Imaging technique</th>
<th>Parameter</th>
<th>Region of interest</th>
<th>Model 1a</th>
<th>Model 2b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>B (95% CI)</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>R², %</td>
<td>R², %</td>
</tr>
<tr>
<td>1H-MRS (n=69)</td>
<td>NAA/Cr ratio</td>
<td>Mid-frontal grey matter</td>
<td>-0.017 (-0.137 to 0.103)</td>
<td>-0.056 (-0.200 to 0.087)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mid-occipital grey matter</td>
<td>-0.013 (-0.113 to 0.088)</td>
<td>-0.021 (-0.144 to 0.103)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left centrum semiovale</td>
<td>0.045 (-0.059 to 0.148)</td>
<td>-0.004 (-0.127 to 0.120)</td>
</tr>
<tr>
<td></td>
<td>Cholr/Cr ratio</td>
<td>Mid-frontal grey matter</td>
<td>-0.013 (-0.033 to 0.007)</td>
<td>-0.008 (-0.031 to 0.016)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mid-occipital grey matter</td>
<td>0.008 (-0.007 to 0.022)</td>
<td>-0.010 (-0.008 to 0.028)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left centrum semiovale</td>
<td>0.015 (-0.004 to 0.034)</td>
<td>-0.000 (-0.023 to 0.022)</td>
</tr>
<tr>
<td></td>
<td>mI/Cr ratio</td>
<td>Mid-frontal grey matter</td>
<td>-0.033 (-0.144 to 0.037)</td>
<td>-0.004 (-0.112 to 0.103)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mid-occipital grey matter</td>
<td>-0.041 (-1.00 to 0.19)</td>
<td>-0.062 (-0.133 to 0.008)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Left centrum semiovale</td>
<td>-0.018 (-0.095 to 0.059)</td>
<td>-0.088 (-0.176 to 0.000)</td>
</tr>
<tr>
<td>Diffusion tensor imaging</td>
<td>FA</td>
<td>Thalamus</td>
<td>-20.09 (-30.91 to -9.27)*</td>
<td>-18.76 (-32.14 to -5.39)*</td>
</tr>
<tr>
<td>(n=68)</td>
<td></td>
<td>Globus pallidus</td>
<td>-10.48 (-31.73 to 10.76)</td>
<td>-14.06 (-40.58 12.47)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Putamen</td>
<td>-10.71 (-25.31 to 3.90)</td>
<td>-8.96 (-26.95 9.03)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caudate nucleus</td>
<td>-14.32 (-29.96 to 1.31)</td>
<td>-15.27 (-34.36 3.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Centrum semiovale</td>
<td>-13.30 (-30.82 to 4.21)</td>
<td>-7.55 (-28.56 13.46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thalamus</td>
<td>-2.18 (-10.8 to 5.43)</td>
<td>2.68 (-1.36 to 6.72)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Globus pallidus</td>
<td>-0.78 (-1.97 to 0.42)</td>
<td>-0.75 (-2.20 to 0.71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Putamen</td>
<td>-0.48 (-1.35 to 0.39)</td>
<td>-0.13 (-1.19 to 0.94)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caudate nucleus</td>
<td>5.22 (0.55 to 10.98)</td>
<td>6.05 (-1.04 to 13.15)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Centrum semiovale</td>
<td>-0.98 (-2.18 to 0.22)</td>
<td>-1.10 (-2.59 to 0.39)</td>
</tr>
<tr>
<td>Perfusion-weighted imaging</td>
<td>rrCBV</td>
<td>Thalamus</td>
<td>0.094 (0.013 to 0.176)*</td>
<td>0.114 (0.007 to 0.220)*</td>
</tr>
<tr>
<td>(n=69)</td>
<td></td>
<td>Globus pallidus</td>
<td>-0.050 (-0.127 to 0.027)</td>
<td>-0.069 (-0.169 to 0.031)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Putamen</td>
<td>-0.006 (-0.063 to 0.052)</td>
<td>-0.010 (-0.083 to 0.063)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caudate nucleus</td>
<td>-0.006 (-0.067 to 0.055)</td>
<td>-0.008 (-0.089 to 0.072)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dorsolateral frontal grey matter</td>
<td>0.056 (-0.002 to 0.114)</td>
<td>0.057 (-0.019 to 0.133)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mid-frontal grey matter</td>
<td>0.052 (-0.019 to 0.122)</td>
<td>0.018 (-0.072 to 0.108)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occipital grey matter</td>
<td>-0.077 (-1.190 to 0.027)</td>
<td>0.038 (-0.089 to 0.165)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Superior parietal grey matter</td>
<td>-0.009 (-0.089 to 0.071)</td>
<td>0.055 (-0.045 to 0.156)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temporal grey matter</td>
<td>0.111 (0.020 to 0.202)*</td>
<td>0.131 (0.013 to 0.249)*</td>
</tr>
<tr>
<td>SPECT (n=47)</td>
<td>[123I]B-CIT binding ratios</td>
<td>Midbrain</td>
<td>-0.106 (-0.326 to 0.113)</td>
<td>-0.092 (-0.373 to 0.188)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thalamus</td>
<td>-0.394 (-0.570 to -0.218)*</td>
<td>-0.343 (-0.566 to -0.121)*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Frontoal grey matter</td>
<td>-0.090 (-0.152 to 0.028)*</td>
<td>-0.038 (-0.136 to 0.023)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occipital grey matter</td>
<td>-0.029 (-0.101 to 0.043)</td>
<td>0.021 (-0.050 to 0.112)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Temporal grey matter</td>
<td>-0.160 (-0.254 to -0.066)*</td>
<td>-0.105 (-0.222 to 0.012)</td>
</tr>
</tbody>
</table>

ADC, apparent diffusion coefficient; Cho, choline; Cr, (phospho)creatine; FA, fractional anisotropy; mI, myo-inositol; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; mI/Cr, regional relative cerebral blood volume; SPECT, single proton emission computed tomography.

a. Linear regression analyses with ecstasy use (dichotomized) as independent variable.
b. Linear regression analyses with ecstasy, amphetamines, cocaine and cannabis use (all dichotomized) as dependent variables, adjusted for covariates.
c. Other than ecstasy.*
P<0.05.
Clusters of significantly lower \[^{123}\text{I}]\text{b-CIT}\) binding ratios in ecstasy users compared with non-users, superimposed on the standard brain.

The thalamic area showed the biggest cluster of significant difference \(Z_{\text{max}}=5.07, P_{\text{corrected, cluster-level}}=0.001;\) coordinates of the highest Z-value: 2, 7, 22. A second significant cluster of decreased \[^{123}\text{I}]\text{b-CIT}\) binding ratios in ecstasy users was observed in the cingulate gyrus, although this should be interpreted with caution, because the highest Z-value was exactly in the midline \(Z_{\text{max}}=4.42, P_{\text{corrected, cluster-level}}=0.007;\) coordinates of the highest Z-value: 0, 42, 8. The clusters posterior on the sagittal slice are related to the upper boundary of the field of view and are likely to represent artefacts rather than real significant differences in \[^{123}\text{I}]\text{b-CIT}\) binding.