Data supplement for Ching et al., Mapping Subcortical Brain Alterations in 22q11.2 Deletion Syndrome: Effects of Deletion Size and Convergence With Idiopathic Neuropsychiatric Illness. Am J Psychiatry (doi: 10.1176/appi.ajp.2019.19030284).

Supplemental Results and Discussion

A. Large A-D Deletion vs. HC Results

Pairwise comparisons of A-D versus HC subjects revealed a similar pattern of ROI differences to that of the full 22q11DS versus HC comparison (**Figure 2; Supplemental Table S14**), likely because ~89% of the 22q11DS sample carried the more common 3Mb A-D deletion subtype.

Subcortical shape analysis revealed a similar pattern of both higher and lower local thickness and Jacobian measures, albeit more spatially confined than the 22q11DS versus HC comparison (**Figure 2**). All effects were robust to adjustment for medication and ROI volume (**Supplemental Table S21; Supplemental Figures F5**).

B. Nested A-B vs. HC Results

Compared to matched HC, subjects with an A-B deletion showed significantly greater ventricle and right accumbens gross volumes (**Figure 2; Supplemental Table S14**). Effects across all ROIs were largely in the same direction as those from the A-D versus HC comparison, indicating similar, though attenuated group differences, likely driven in part by the much smaller A-B sample size (N=18). When adjusting for medication, no group differences surpassed multiple comparison correction (**Supplemental Table S22**).

Subcortical shape analysis results revealed a more extensive, though subtle, pattern of differences between A-B deletion cases and HC (**Figure 2**). Specifically, higher accumbens gross volumes were likely driven by higher Jacobians (surface dilation) in A-B subjects. Results were diminished when correcting for ROI volume and medication, likely due to reduced power (**Supplemental Figures F6**).

C. Discussion of Thalamic and Caudate Results

Subjects with 22q11DS had greater SA and thickness in thalamic subregions roughly corresponding to anterior, dorsomedial and ventral lateral nuclei, but lower thickness and SA in the pulvinar, a region that receives input from — and projects to — the parietal, occipital and temporal lobes. Both the pulvinar and the dorsomedial nucleus make up the principal association nuclei of the thalamus, with projections to cortical association areas that mediate many higher-order cognitive functions. Notably, 22q11.2 mice show disrupted

synaptic transmission at thalamocortical glutamatergic projections in auditory cortex, which is hypothesized to play a role in auditory hallucinations in 22q11-associated psychosis (1).

With respect to the caudate, 22q11DS subjects had, on average, greater thickness and SA in more anterior (head) and lateral portions of the caudate, and lower thickness and SA in more posterior (body/tail) regions, compared to HC. As the caudate receives most of its input from cortical association areas, particularly the prefrontal cortex (2), differential alterations to these caudate subregions may impact connectivity of fronto-subcortical networks.

References:

1. Chun S, Westmoreland JJ, Bayazitov IT, et al.: Specific disruption of thalamic inputs to the auditory cortex in schizophrenia models. Science 2014; 344:1178–82

2. Kotz SA, Anwander A, Axer H, et al.: Beyond cytoarchitectonics: the internal and external connectivity structure of the caudate nucleus. PLoS One 2013; 8:e70141