Striatal volume and functional connectivity predict weight gain in early-phase psychosis

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Background

- Weight gain is a major side effect of treatment with antipsychotic drugs
- The dorsal striatum plays a key role in the human reward system and in appetite regulation
- We measured striatal volume and striatal resting state functional connectivity at baseline (Fig. 1), and weight gain over the course of 12 weeks of antipsychotic treatment in 81 patients with early-phase psychosis (Fig. 1, 2)

Methods: Baseline imaging

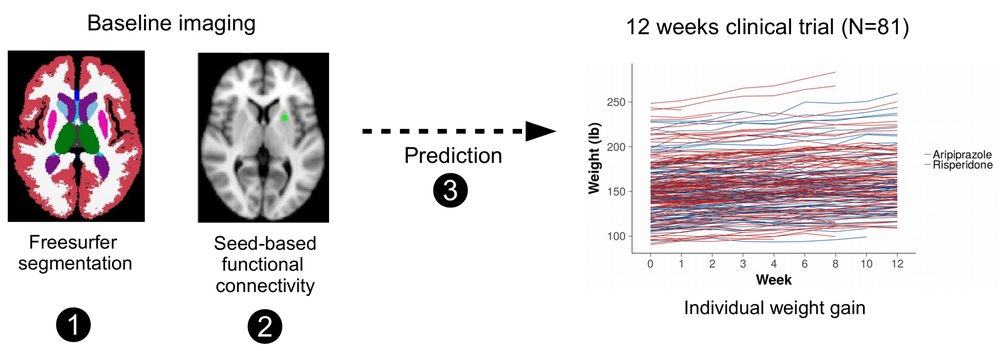

Figure 1: Analysis flow chart. We measured striatal volume and striatal resting state functional connectivity at baseline, and weight gain over the course of 12 weeks of antipsychotic treatment in 81 patients with early-phase psychosis. We also included a sample of 58 healthy controls. Weight measurements were completed at baseline, and then weekly for 4 weeks, and every 2 weeks until week 12. We used linear mixed models to compute individual weight gain trajectories. Striatal volume and whole-brain striatal connectivity were then calculated for each subject, and used to assess the relationship between striatal structure and function and individual weight gain in multiple regression models.

Methods: Individual weight gain slopes

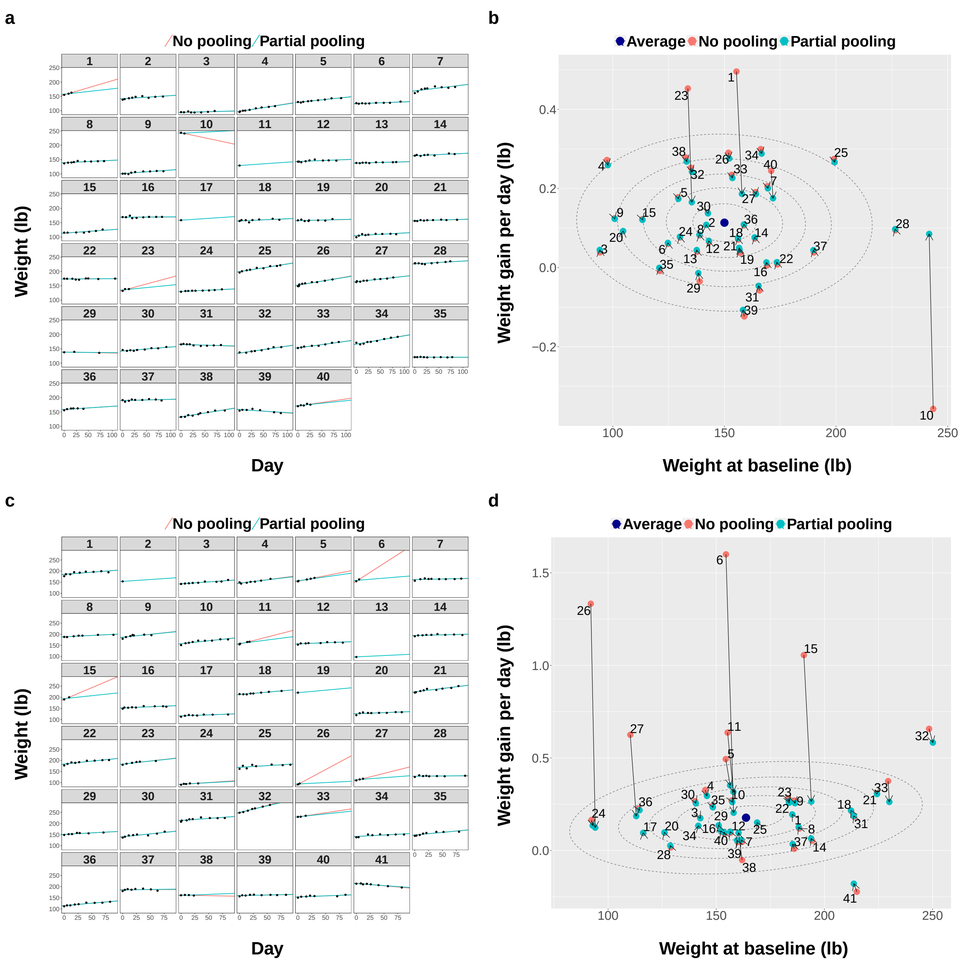

Figure 2: Partial pooling to regularize individual weight slopes. a. Individual time courses for all participants from the first schizophrenia cohort. Partial pooling regularized the individual slopes, i.e., the influence of outliers with only few assessments was attenuated. **b. The partial pooling effect is demonstrated by the individual weights being pulled toward the average treatment effect.** As a consequence, outliers are less influential. **c, d. The same is shown for the second schizophrenia cohort.** Dotted ellipses indicate confidence regions for the average treatment effect.

Results: Striatal volume

- The left putamen volume predicted magnitude of weight gain (Fig. 3a) in patients (β = 0.31, t (68) = 2.18, P = 0.032; Fig. 3b)
- Decreased functional connectivity with the left medio-lateral frontal pole also predicted amount of weight gain (Fig. 4a, b)
- An interaction of volume and connectivity (β = -0.38, t (65) = -3.36, P = 0.001; Fig. 4c) suggested that the negative relationship between fronto-striatal connectivity and weight gain was weaker for lower compared to higher striatal volumes

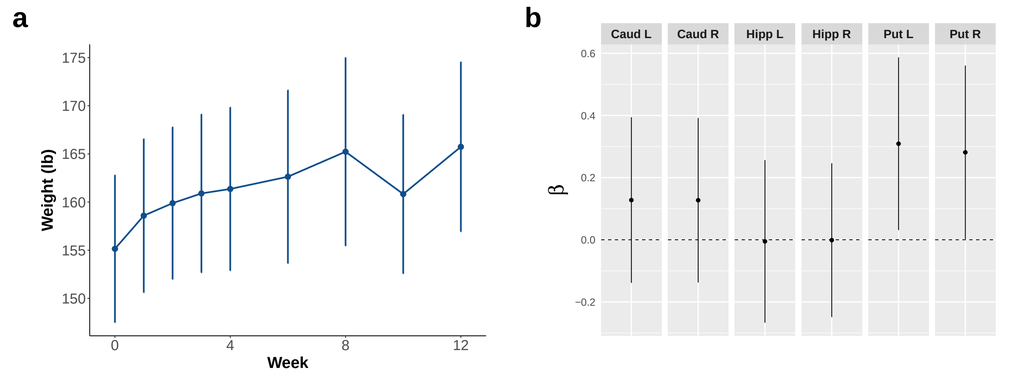

Figure 3: Striatal volume predicts weight gain in schizophrenia patients (N = 81). a. Weight increased significantly over the course of the trial. Means with 95% confidence intervals are shown. **b. Weight gain in patients was predicted specifically by the left putamen volume.** Standardized beta coefficients with 95% confidence intervals are shown. All models were adjusted for age, sex, age-by-sex, duration of untreated psychosis, intracranial volume, and body mass index, none of which were significant predictors of weight gain. Error bars not touching the zero line indicate significant effects (P < 0.05). *Abbreviations*: Caud, caudate; Hipp, hippocampus; Put, putamen; L, left, R, right.

Results: Fronto-striatal connectivity

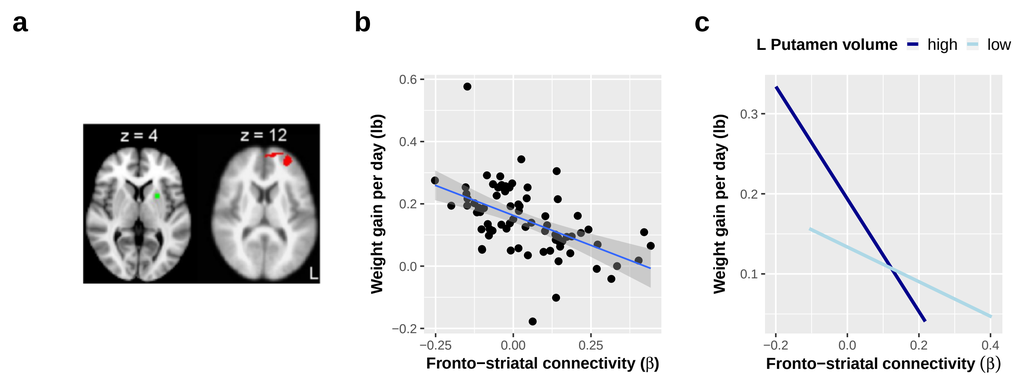

Figure 4: Fronto-striatal connectivity and the interaction of striatal structure and function predict weight gain in early psychosis patients (N = 75). a, b. Lower functional connectivity between the left putamen and the left frontal pole predicted weight gain. Following up on the left putamen volume finding, we tested for functional connectivity between the left putamen and the whole brain that was associated with weight gain. The left dorsal rostral putamen (green) was used as seed region, and the left frontal pole (red) was the only connected region surviving a voxel level threshold of z > 3.1 and a cluster threshold of P < 0.05. **c. Interaction of striatal structure and function in predicting weight gain.** To illustrate the significant interaction between left putamen volume and connectivity, we plotted regression lines for weight gain and connectivity for the highest quartile (25%) of putamen volume and the lowest quartile (25%) of putamen volume.

Conclusions

- These results provide evidence for a synergistic effect of striatal structure and function on antipsychotics-induced weight gain
- Lower fronto-striatal connectivity, implicated in less optimal long-term decision making, was associated with more weight gain, and this relationship was stronger for higher compared to lower left putamen volumes

Disclosure

Dr. Robinson has served as a consultant for Asubio, Otsuka, and Shire and has received grants from Bristol-Myers Squibb, Janssen, and Otsuka. Dr. Lencz is a consultant for Genomind. Dr. Malhotra has served as a consultant for Forum Pharmaceuticals and has served on a scientific advisory board for Genomind. The other authors report no financial relationships with commercial interests.

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