**Background:** Evidence from candidate-gene and epigenome-wide studies suggests that epigenetic alterations may contribute to the demonstrated relationship between maternal prenatal depression and adverse offspring outcomes. Preliminary studies indicate that maternal prenatal depression may lead to “epigenetic age deceleration” in newborns, which in turn has been suggested as a risk factor for later developmental delays and psychopathology. Replication of these studies is warranted, as is further empirical testing of potentially co-occurring maternal risk factors including elevated rates of stress and antidepressant use in pregnancy.

**Methods:** The present study examined the relationship between maternal prenatal exposures (i.e., depression, stress, and SSRI use) and offspring epigenetic age deceleration in a prospective cohort of mother-offspring dyads (n=303). Mothers were recruited from the Emory Women’s Mental Health Program in the first trimester of pregnancy and followed longitudinally until delivery. Offspring epigenetic age was determined via cord blood samples.

**Results:** Findings indicated that maternal prenatal stress was unrelated to newborn epigenetic age (p=0.51). Maternal prenatal depression was associated with decelerated epigenetic age in newborns (p=0.03), but this relationship was not significant when statistically controlling for maternal use of SSRIs (p=0.41). Conversely, maternal SSRI use in pregnancy significantly predicted newborn epigenetic age deceleration over and above the influence of maternal depression (p=0.001).

**Conclusions:** These findings suggest that maternal prenatal SSRI use may significantly contribute to the previously documented associations between maternal prenatal depression and epigenetic age deceleration. Further studies are needed to examine how these epigenetic differences at birth may contribute to adverse outcomes in later development.

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**Keywords:** Epigenetics, Prenatal Depression, SSRI, Prenatal Exposure, Epigenetic Biomarkers

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**Measuring and Estimating the Effect Size of Rare Non-Recurrent Deletions and Duplications on General Intelligence**

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**Background:** Copy number variants (CNVs) classified as pathogenic are identified in 10 to 15 % of patients referred for neurodevelopmental disorders. However, their effect sizes on cognitive traits measured as a continuum remain mostly unknown because the vast majority of them are too rare to be studied individually. Our objective is to measure and predict the effect of CNV on IQ.

**Methods:** We called CNVs ≥50Kb from genotyping data with PennCNV and QuantiSNP in 21,393 individuals of 5 general population cohorts as well as two disease cohorts. General intelligence was measured using different IQ scales or general factor. Linear and non-linear models investigated functional annotations of genes included in CNVs to identify features explaining their effect size on IQ. Validation was performed using intra-class correlation comparing IQ predicted by the model to empirical data.

**Results:** Among 10 functional annotations, the probability of being intolerant to haplinsufficiency(pLI) is best to explain the effect of deletions on IQ with a decrease of 2.6 points per unit of pLI(p<10-28) and for duplications, decrease of 0.75 points of PIQ per unit of pLI(p<10-9). Effect-size of CNVs was similar across all methods used to measure general intelligence and across cohorts. The concordance analysis between model estimates and observed effects from previous publications is >75%.

**Conclusions:** The effect-size of CNV on general intelligence can be reliably estimated across the genome. This represents a framework to study variants too rare to perform individual association studies and we provide a new online tool for clinicians to estimate the contribution of undocumented CNVs.

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**Keywords:** Genetics, CNV, Intelligence

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**Meta-analysis is Consistent With Dopaminergic Perceptual and Cognitive Prediction Errors**

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**Background:** Reward Prediction error (PE) signals occur to unexpected outcomes and drive new learning. Their aberration has been implicated in the pathophysiology underlying many psychiatric syndromes. PE theory has been extended beyond reward to perception and cognition, which is relevant to explaining psychotic symptoms. Here we meta-analyze functional neuroimaging studies of prediction error to examine one key prediction of this extension, that dopaminergic prediction error signals not only only underwrite reward learning but also perceptual and cognitive inferences.

**Methods:** We performed a quantitative neuroimaging-based meta-analysis summarizing results from 252 published functional magnetic resonance imaging studies of PE. Extracted XYZ coordinates and meta-data (e.g., PE type) were extracted and analyzed using state-of-the-art multi-level kernel-based density analysis. All results were familywise error corrected at p<.05.

**Results:** Across all included studies, PEs engaged striatum, midbrain, dorsal prefrontal cortex, anterior and posterior cingulate, and insula. Studies reporting positive PEs (Nstudies = 52) consistently engaged the striatum, midbrain, and insula. Studies reporting negative PEs (Nstudies = 29), consistently
engaged the striatum, midbrain, anterior cingulate, and insula. Both traditional reward PEs and PEs related to violations of perceptual or cognitive expectations engaged the striatum and midbrain.

**Conclusions:** Prediction errors engage regions associated with learning, dopamine, and executive networks, as well as limbic and association cortices. The striatum and midbrain were engaged by reward PEs and to violations of cognitive and perceptual expectations. This is consistent with predictive processing theories in psychiatry, and recent preclinical work suggesting the engagement of the dopamine system in learning perceptual associations.

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**Keywords:** Reward, Prediction Errors, Meta-Analysis, Functional Imaging, Learning

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**Microscopic Structure of Frontal White Matter Predict Delay Discounting**

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**Background:** Delay discounting refers to the preference for smaller and sooner rewards over larger and later ones. Exaggerated delay discounting is a robust transdiagnostic process across a range of psychiatric disorders. However, its neurobiological underpinnings are not well understood with many inconsistencies in the literature of its structural correlates.

**Methods:** We leveraged a large openly available dataset (n=1196) to robustly unveil gray and white matter correlates of delay discounting. We decomposed the grey matter density images and fractional anisotropy skeleton maps separately into 50 components using independent component analysis. We tested for associations between delay discounting and grey matter and white matter components using linear models. Significance was tested with non-parametric permutation tests and family-wise error rate control for multiple tests using the distribution of the maximum statistic.

**Results:** Greater delay discounting was related to smaller grey matter density in anterior temporal cortex and greater frontal fractional anisotropy, a marker of white matter microscopic organization. Effects of the structural predictors of delay discounting were small. This may explain the incongruities in the literature because the effects would be unlikely to be replicated in a sample of size comparable to that used in many previous studies. Accordingly, only the strongest association, between frontal FA and delay discounting, was replicated in a second independent sample (n=60).

**Conclusions:** These results help reconcile disparities in the literature on gray and white matter correlates of temporal discounting and point to decreased complexity of frontal white matter's microscopic organization as a predictor of higher delay discounting.

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**Keywords:** Delay-Discounting, White Matter, Grey Matter Density

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**Mindfulness-Based Cognitive Therapy Attenuates Default-Mode Network Connectivity in Patients With Clinically Significant Anhedonia**

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**Background:** Mindfulness practice is increasingly understood to have a beneficial role in treatment of psychiatric disorders. Mindfulness impacts brain networks involved in sustained attention (i.e., the frontoparietal network-FPN) and self-reflective thought (i.e., the default-mode network-DMN) partly by altering resting-state functional connectivity (RSFC). However, few studies to date have used RSFC to evaluate therapeutic effects of mindfulness in psychiatric populations.

**Methods:** Fifty-six adults (18–49 years old; 44 female), with clinically significant anhedonia and a variety of DSM5 diagnoses were randomized to 15 weeks of Mindfulness-Based Cognitive Therapy (MBCT) or Behavioral Activation Therapy for Anhedonia (BATA). 7-Tesla fMRI scans were acquired to assess RSFC at baseline, once or twice during treatment, and at post-treatment for a total of 163 scans after removing motion outliers. Average RSFC within DMN & FPN at each time point was calculated using CONN toolbox and multilevel models were run using the lme4 package in R to evaluate treatment by time interaction effects on connectivity.

**Results:** Unconditional growth model (random intercepts and random slopes) showed a trend towards decreasing DMN connectivity with time (p=0.07) across both groups. There was a significant treatment by time interaction (p=0.03) such that MBCT was associated with greater decreases in average DMN connectivity compared to BATA. Including the interaction term explained an additional 24% of the variance between individuals. There were no significant changes in FPN connectivity.

**Conclusions:** MBCT attenuates DMN connectivity compared to BATA. DMN connectivity may be a useful biomarker to evaluate the therapeutic effects of mindfulness practice in patients with clinically significant anhedonia.

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**Keywords:** Mindfulness, Default Mode Network, Behavioral Activation, Anhedonia, fMRI

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**Mitochondrial Respiratory Chain Function in Major Depression**


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