In This Issue

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A brief summary of the articles appearing in this issue of *Biological Psychiatry*.

Review: Neural Circuits and Oxytocin

Oxytocin (OT) promotes social interactions but can also induce social anxiety. In this review, **Steinman *et al.*** (pages 792–801) provide evidence that distinct but overlapping neural circuits mediate these diverse actions of OT. The authors propose that OT effects in the nucleus accumbens and ventral tegmental area may promote social approach behavior, whereas OT effects in the bed nucleus of the stria terminalis may induce social avoidance. They conclude that future evaluations of OT-based therapeutics should utilize preclinical findings and consider a broader range of behavioral and neural outcome measures.

Mechanisms of OT's Anxiolytic Effects

OT has anxiolytic properties, mediated in part by intracellular signaling pathways coupled to the OT receptor, but understanding of the underlying molecular mechanisms remains incomplete. Using a combination of behavioral, biochemical, and pharmacological approaches, **Martinetz *et al.*** (pages 802–811) shed further light on the pathways recruited for OT-mediated anxiolysis. They report that OT stimulates protein synthesis via eukaryotic elongation factor 2 within the hypothalamic paraventricular nucleus. Further, they identified the protein synthesis of neuropeptide Y receptor 5 as crucial for OT's anxiolytic effects. These data indicate that eukaryotic elongation factor 2 may represent a novel target for the treatment of anxiety disorders.

Chronic Stress Effects on Amygdala Neurons

Activation of basolateral amygdala projection neurons (BLA PNs) contributes to stress-related disorders. However, BLA PNs are organized into distinct output circuits, and it remains unclear whether stress differentially influences these subpopulations. In this study, **Zhang *et al.*** (pages 812–828) found that chronic restraint stress causes persistently increased neuronal excitability in BLA PNs projecting to the ventral hippocampus, but not in those projecting to the medial prefrontal cortex or nucleus accumbens. The authors then linked this activation to downregulation of small-conductance, calcium-activated potassium (SK) 2 channel currents. Viral overexpression of SK2 channels in this subpopulation prevented stress-induced anxiety-like behavior. These data reveal projection-specific functional adaptation of BLA PNs following chronic stress.

Longitudinal Analysis of Depression and Inflammation

The link between inflammatory markers and depression is well established, but most studies have been cross-sectional. Using data from a longitudinal cohort study, **Lamers *et al.*** (pages 829–837) observed cross-sectional and longitudinal associations between interleukin-6 (IL-6) levels and current depressive disorder in adults. Higher IL-6 levels predicted chronicity in women with a diagnosis of depression at baseline, and a depressive disorder diagnosis predicted higher IL-6 levels at follow-up. C-reactive protein showed no association with depression. These data highlight that IL-6 may have value as a potential marker for personalized treatment approaches in depression.

Early-life Adversity: DNA Methylation and Hippocampal Volume

Exposure to early-life adversity (ELA) is known to predict epigenetic patterns that may be related to psychiatric risk, but few studies have investigated whether adversity has time-dependent effects. Using data from a prospective, longitudinal study, **Dunn *et al.*** (pages 838–849) tested whether there are sensitive periods when adversity exposure induces greater epigenetic differences. The authors found that the developmental timing of adversity, particularly exposures before age 3, explained more variability in DNA methylation at age 7 than the accumulation or recency of exposure. These results suggest that very early childhood may be a vulnerable period during which exposure to adversity may have greater influence on alterations in DNA methylation patterns.

ELA increases risk for major depressive disorder (MDD) and suicide, which have been associated with smaller dentate gyrus (DG) and fewer granule neurons. **Boldrini *et al.*** (pages 850–862) analyzed hippocampal postmortem tissue in people with ELA who were resilient to psychiatric illness and in people with MDD who died by suicide with or without exposure to ELA. Resilient individuals had larger DG volume. Subjects with MDD but no ELA showed smaller DG volume, fewer granular neurons, and fewer neural progenitor cells, compared with non-ELA control subjects. ELA was associated with more granular neurons in both exposed groups. These data suggest a link between resilience to ELA and larger DG volume.

Predicting Treatment Response in Depression

Early childhood depression is associated with anhedonia and reduced brain responses to rewarding and pleasant stimuli, but whether these measures change with treatment or predict treatment response is unclear. **Barch *et al.*** (pages 863–871) analyzed event-related potentials in young depressed children before and after 18 weeks of a parent-child psychotherapy or waitlist. Children randomized to the therapy showed greater reduction in anhedonia and increased reward positivity responses. Greater change in reward positivity was associated with greater symptom reduction. Further, greater brain responses to pleasant pictures prior to treatment predicted a higher likelihood of response to therapy. These data suggest that event-related potential measures may be useful to identify children who may benefit the most from emotion development therapy.

Pretreatment activity of the rostral anterior cingulate cortex (rACC), a hub of the default mode network, has emerged as a predictor of antidepressant response. Using data from a clinical trial in patients with MDD, **Whitton *et al.*** (pages 872–880) examined whether rACC connectivity with other brain networks may drive this link. They report that increased connectivity between the rACC and the right anterior insula, a salience network hub, predicted greater depression improvement following both sertraline and placebo treatment, and also predicted remission likelihood. These findings indicate that rACC-salience network connectivity may represent a useful predictor of the degree to which depressive symptoms are responsive to intervention.

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