

(sleep) and molecular mechanisms involved in contextual processing deficits.

Methods The evolution of functional neuroimaging studies from early studies of responses to emotional probes to recent multi-day studies of fear conditioning, extinction, renewal, and of intrinsic connectivity networks, will be discussed and novel findings presented. Parallel findings from studies using Single Prolong Stress model of PTSD in rodents will be discussed further dissecting molecular mechanisms in prefrontal, hippocampal and LC regions.

Results PTSD subjects exhibit unimpaired fear conditioning and extinction, but altered psychophysiology and prefrontal and hippocampal BOLD responses during fear renewal and reinstatement, pointing toward abnormalities in contextual processing. In parallel, exaggerated fear renewal is present in SPS animals, especially these with increased REM and decreased hippocampal theta power. Molecular studies link upregulation in glucocorticoid receptors (GR) in hippocampus and prefrontal cortex to exaggerated fear renewal.

Conclusions Converging findings from human neuroimaging studies and animal models implicate contextual processing abnormalities in PTSD. Animal model implicate upregulation of GR receptors in mPFC and hippocampus, changes in noradrenergic tone in LC, and in norepinephrine dependent sleep parameters, in these context-processing deficits. Together these studies transform our understanding of PTSD pathophysiology suggesting a more complex and nuanced model of pathophysiological processes leading to PTSD.

Speaker 2: Talma Hendler, Israel

Title: Neural indication of stress regulation: from biomarkers to treatment targets

Abstract

Stress regulation has been formulated lately as a result of balanced shift between neural systems involved in salience and cognition. It is yet unclear what determines the individual ability to achieve such balance and adaptively recover from a stressful event. We have asserted that identifying such neural elements could provide effective targets for control training, and improved stress resilience. Using prospective neuroimaging approach we demonstrated in a recent study that soldiers, prone to intense and often traumatic stress, differ in their tendency to recruit ventro-medial PrefrontalCortex (vmPFC) under angering social situation (Gilam et al 2016). Further, this regulation ability that has enhanced their resilience, was mediated by miRNA fold change (Vaisvaser et al 2016). This intriguing findings complement previous work in our lab showing that greater vmPFC recruitment following trauma exposure was correlated with lower amygdala reactivity prior to exposure, suggesting their opposing dominance in stress regulation (Admon et al 2009). Taken together, accumulating evidence point to the role of either down regulating limbic nodes or upregulating PFC node as a mean for stress inoculation. Using closed-loop brain-machine interface that is based on fMRI inspired EEG (see Keynan et al 2016), we trained soldiers to self-regulate their amygdala activation. Most of the soldiers have learned to successfully down-regulated their amygdala activation during training sessions as well as on a transfer trial without feedback. Furthermore, following repeated training sessions, the trained soldiers exhibited improved performance on emotional stroop task and greater connectivity between the amygdala and vmPFC, suggesting improved emotion regulation. The usage of advanced BCI (Cavazza et al 2014, Keynan et al 2016) in light of neuroscientific

insights for early treatment in stress related disorders will be considered and discussed.

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Speaker 3: Saori Tanaka, Japan

Title: Neurocomputational model for reward prediction and decision making in psychiatric disorders

Abstract

To elucidate complex brain function, a computational approach is widely accepted in system neuroscience as well as clinical disciplines. In particular, computational models of neuromodulators, such as dopamine and serotonin, are indispensable to make clear the neural system of prediction and decision-making, and these models have been frequently tested using an experimental approach.

Prediction error signal in reinforcement learning theory is a representative computational model for the role of dopamine in prediction and decision-making. This model was proposed on the basis of electrophysiological data from a series of studies on dopaminergic neurons in monkeys conducted by Schultz et al. in the 1990s (Romo and Schultz 1990; Mirenowicz and Schultz 1994, 1996). In classical conditioning experiment, dopaminergic neurons in monkeys responded to rewards before learning, whereas after the learning tasks, these neurons started to respond to the conditioned stimuli. This neuronal alteration observed in dopaminergic neurons was revealed to be similar to the prediction error signal in reinforcement learning (Sutton and Barto 1998). Based on this new discovery of the role of dopaminergic neurons, reinforcement learning model mediated by the cortico-basal ganglia circuit has been proposed (Houk 1994), and this model is supported by studies using electrophysiological techniques and functional magnetic resonance imaging of human brain (Schultz, Dayan and Montague 1997; O'Doherty et al., 2003).

The representative role of serotonin in prediction and decision-making may be "impulsive choice" behavior. Impulsive choice is defined as a behavioral preference of immediate small rewards over distant large rewards (Ainslie 1975), and rats

developed impulsive choice behavior when the serotonergic system in the brain was destroyed (Wogar et al., 1993; Poulos et al., 1996; Mobini et al., 2000). On the basis of these findings, it has been proposed that serotonin is involved in delay discounting. However, because serotonergic neurons have a wide range of projection and a large number of serotonin receptor subtypes exist, many questions remain about the functional role of serotonin in impulsive choice. Consequently, various computational models of serotonin (Daw, Kakade and Dayan, 2002), including temporal discounting (Doya 2002), have been proposed and are being investigated (Tanaka et al., 2007, 2009).

Recently, we applied this computational approach to patients with obsessive-compulsive disorder (OCD) and attention-deficit hyperactivity disorder (ADHD). We found that patients exhibited different choice behavior and different neural activities from those of healthy controls in delay discounting tasks. The application of computational techniques in clinical research has been attracting attention in recent years. Current disease classifications based on symptomatology are greatly affected by biological heterogeneity, and their pathogenesis is difficult to elucidate by, for example, gene analysis, which makes the development of therapy based on etiology difficult. The use of computational techniques is expected to overcome this problem and we believe our approach described here will contribute to achieving this goal.

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Speaker 4: Go Okada, Japan

Title: Cortisol modulation of emotion regulation neurocircuits in PTSD

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Abstract

Objectives: There is growing evidence that many emotion-regulation processes operate at implicit levels, and the ability to regulate emotions without the need for conscious effort is important for mental health. The glucocorticoid hormones (cortisol in humans) are crucial for stress responses and adaptation, and posttraumatic stress disorder (PTSD) has been associated with both cortisol dysregulation and abnormalities in brain regions involved in emotion regulation. However, how cortisol affects implicit emotion regulation in PTSD, until now has not been studied. In the present study, we examined the effects of exogenous synthetic cortisol (hydrocortisone, HCT) administration on emotion regulation neurocircuits in individuals with and without PTSD.

Methods: Here, we used administration of HCT, functional magnetic resonance imaging (fMRI) and the shifting emotion

appraisal task (SEAT) which probes neurocircuits of two types of implicit emotion regulation i.e., attention shifting and cognitive appraisal to examine the effect of cortisol on emotion regulation neurocircuits. Using counter-balanced, placebo-controlled, double-blind, within-subject design, 11 individuals diagnosed with PTSD and 11 healthy controls were scanned with blood-oxygen-level-dependent sensitive whole-brain fMRI on 3.0 Tesla GE Signa System, while performing the SEAT on two separate occasions, once following 100mg HCT administration and once following Placebo administration. Preprocessing of fMRI data and analyses were conducted in Statistical Parametric Mapping 8 (SPM8; the Wellcome Trust Centre for Neuroimaging).

Results: Experimental manipulation robustly activated neurocircuits involved in emotional regulation by attention shifting and cognitive appraisal respectively. Shifting attention to background context resulted in significant activation in the place processing areas such as parahippocampal place area and attention control areas such as dorsolateral PFC. Cognitive appraisal elicited significant activity in the broad area of medial and left lateral PFC. Differential cortisol modulations of task related activation were observed in the hippocampus and subgenual anterior cingulate cortex (sgACC) between in controls and in patients with PTSD. The left hippocampus activation during shifting attention to background context was decreased by HCT administration in patients with PTSD while increased in Controls. Differential activation during cognitive appraisal was significant in the sgACC, and this effect is mainly driven by enhanced activation of this area by HCT administration in patients with PTSD.

Conclusions: We used a probe of the implicit emotion regulation processes to assess how cortisol affects the emotion regulation neurocircuits, and demonstrated that elevation of cortisol is associated with reduced activity in the hippocampus during shifting attention to background context and increased activity in the sgACC during cognitive appraisal only in patients with PTSD. These results suggest that the way hormonal activity affects the brain regions involved in emotion regulation is altered in patients with PTSD, possibly reflecting altered sensitivity of the glucocorticoid receptor in these regions in patients with PTSD.

S27: CINP –ICGP Panel Molecular Mechanisms of Late Life Mood and Cognitive Disorders: Targets for Prevention and Intervention

Chair: Gwenn Smith, USA

Co-Chair: Jeong Lan Kim, Republic of Korea

Speaker 1: John O'Brien, UK

Title: Neuroinflammatory changes in late life depression: the NIMROD study

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