S25: The CINP bipolar algorithm project

Chair: Hans Jürgen Möller, Germany
Co-Chair: Andi Tanra, Indonesia

Speaker 1: Hans Jürgen Möller, Germany
Title: Are everyday clinical practice and guideline supported clinical decision making in contrast?

Abstract
Among psychiatrists there is a common feeling, that guidelines directives on psychopharmacological treatment are often in contrast to clinical decision making driven by clinical experience. This might be one reason, why compliance to guidelines is not as one might expect.

Reasons for this discrepancy are related among others in the way guidelines are developed by the respective commissions: the experts are often not or not any more clinically experienced, the priority given to meta-analyses lead to relative global results, for more differentiated treatment problems (drug resistance, predominance of certain sub-syndromes, psychiatric and non-psychiatric comorbidity, co-medication etc.) Sufficient data are not available, individual dispositions of the patients are not sufficiently considered in the EBM data base, the gap between phase-1 studies and phase-4 studies is difficult to overcome.

The current position of EBM neglects extremely the value of clinical practice and is not open enough for more critical reflections about is own methodological limitations. Especially the one-sided preference for meta-analyses should be replaced by a multi-methods approach, involving much more the evaluation of individual studies. This would help among others to give answers also to questions mentioned above, so far mostly not addressed sufficiently by the available guidelines.

Abstract
The CINP assembled a workgroup to develop guidelines and a precise algorithm for Bipolar disorder (BD). The works are still in progress and the actual guideline is expected to be published within 2016. These guidelines will be based on hard data and were intended to be as evidence based as possible. A new system of grading the evidence was developed. Monotherapy was given priority over combination therapy. The first approach led to draft detailed guidance for each phase of BD in a five-step way, by taking into consideration the specific clinical features if possible.

The second includes a very precise algorithm. When released, the CINP guidelines will be the most recent fully updated and fully evidence based guidelines on the treatment of BD. Many issues need further study, data are rare and insufficient and many questions remain unanswered. The most important and still unmet need is to be able to merge all the guidelines which concern different phases of the illness into a single one, and in this way consider BD as a single unified disorder, which is the real world fact. However to date the research data do not permit such a unified approach.

Speaker 2: Konstantinos N Fountoulakis, Greece
Title: The Collegium International Neuro-Psychopharmacologicum (CINP) treatment guidelines for bipolar disorder in adults

S26: Modulation of emotion in psychiatric disorders

Chair: Go Okada, Japan
Co-Chair: Anton J M Loonen, Netherlands

Speaker 1: Israel Liberzon, USA
Title: Contextual modulation of fear in PTSD

Abstract
Background; The brain mechanisms that underlie PTSD are not yet understood. We had proposed that deficits in the processing of contextual information are at the core of PTSD pathophysiology, and they involve complex interplay between fear associated learning, memory, sleep, hyperarousal and stress responses in PTSD. We performed genetic and functional neuroimaging studies in PTSD subjects as well as translational studies in animal model of PTSD, to identify brain regions, as well as physiological
(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 finding 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 implicates 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...