

**S1** *New frontiers of psychotherapy research: a quest for the future*

**A COGNITIVE NEUROSCIENCE PERSPECTIVE ON THE DIAGNOSIS OF SCHIZOPHRENIA**

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**Objective:** The decade of the brain is more than halfway through, and hardly a month passes by without breathtaking news from the field of neuroscience and cognitive neuroscience. Particularly the advent of the latter - a merger of psychology, neurobiology, computer science, linguistics, philosophy and anthropology - in the recent past provided for the first time, the background for a conjoint view of mind and brain. This situation provides a challenge for psychiatrists eager to understand their patients within such a unitary framework. The incredible amount of new data and the detail of available information make it hard for the non-neuroscientist to filter out what is most conceptually useful and possibly clinically applicable.

**Method:** Concepts from (cognitive) neuroscience will be discussed and applied in the field of psychiatry, guided by the following questions: Which concepts are important for psychiatric diagnosis? How can they be applied to psychopathological phenomena and psychiatric disorders? What can be gained from (cognitive) neuroscience within psychiatry?

**Results:** The presentation will focus on the concepts of neuroplasticity and neuromodulation, and examples from psychopathology - hallucinations, delusion, formal thought disorder and affective pathology illustrate the main point of the paper, i.e. that neuroscience is relevant to psychiatry, in particular to psychopathology and diagnostic concepts.

**Conclusions:** The unitary cognitive neuroscience framework should have a major impact upon diagnostic habits in psychiatry, since it is incompatible with strong divisions between the psychological and the physiological. Likewise, the border between developmental and personality disorders and the "classic" mental disorders becomes increasingly blurred.

**S2** *Mechanisms and treatments of opioide addiction*

**Clinical pharmacology and efficacy of new drugs for treatment of opioide dependence**

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To prevent, suppress or alleviate opioid withdrawal symptoms, short-term detoxification usually involves the administration of opioid agonists (i.e. methadone, dextropropoxyphene, buprenorphine) or alpha-2-adrenergic agonists (i.e. clonidine, guanfacine, lofexidine). New ultrarapid detoxification schedules include the induction of acute withdrawal by naloxone under sedation (midazolam, antiemetics) and rapid transfer to the antagonist naltrexone. Although short-term efficacy seems satisfactory in selected individuals, the precipitated withdrawal syndrome can be dangerous and there are no published reports on the relapse rate or long-term outcome. Long-term treatment includes opioid agonist maintenance programs or the use of opioid antagonists. Methadone maintenance programs (MMP) are the standard alternative, having being promoted in most countries in relation to AIDS epidemics. Levocacetyl-alfa-methadol (LAAM) or bilingual buprenorphine are other drugs that have been investigated and marketed in some countries to substitute methadone in the long-term treatment. LAAM is a full opioid agonist that could be given orally every 2 to 3 days. LAAM seems an effective drug, but its clinical dossier is lacking of controlled clinical trials using methadone as the reference drug. The partial opioid agonist buprenorphine seems to be a useful drug, but it is not free of abuse potential. Poor results have generally been obtained in naltrexone-based long-term programs, although this modality of therapy can be useful in highly selected populations.

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**DSM-IV SCHIZOPHRENIA DIAGNOSIS IN GENERAL PSYCHIATRIC SERVICES: DO EMPIRICAL CONSTRUCTS MEET CLINICAL REALITIES?**

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**Significance:** More research should assess how carefully ordinary clinicians utilize the new diagnostic classifications (ICD-10, DSM-IV) in the field of Schizophrenic Disorders. Specifically, these studies should determine whether ICD/DSM Schizophrenia diagnosis and treatment by clinicians are in agreement with the corresponding ICD/DSM constructs.

**Methods:** We investigated 97 patients, aged 18-65, referred with psychotic symptoms and treated for at least 15 days at the in-patient department of Geneva University Psychiatric Centre. Each subject had DSM-III-R diagnostic assessments by an attendant psychiatrist and an independent SCID interview by a clinical psychologist. Treatment and course were recorded on a distinct form. Clinicians had repeated informal interviews to determine how carefully they utilized DSM-III-R.

**Results:** When compared to SCID diagnoses, clinician's DSM-III-R diagnoses indicated more Schizophrenic Disorders, less Mood Disorders and less absence of Psychotic Disorders. Treatment reviews indicated long-term neuroleptic treatment choice for a very large majority of subjects. Clinician's assessment neglected criteria review for each DSM-III-R syndrome addressing DSM-III-R Disorders as concrete categorical entities instead of empirical constructs.

**Comment:** The present data indicated that well trained clinicians did not carefully assess and did not correctly understand DSM-III-R Schizophrenia despite intensive training and formal adherence to DSM diagnostic classification, they still utilized a classic, overinclusive Schizophrenia construct. In the clinical arena, Schizophrenia diagnosis mediates scientific, medical and care management models.

**S2** *Mechanisms and treatments of opioide addiction*

**Use of antisense oligodeoxynucleotides to characterize G proteins activated by  $\mu$ - and  $\delta$ -opioid agonists *in vivo***

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Subchronic intracerebroventricular administration of end-capped phosphorothioate antisense oligodeoxynucleotides (ODNs) to  $G\alpha$  subunit mRNAs were used to impair the function of mouse  $G_{i1}$ ,  $G_{i2}$ ,  $G_{i3}$ ,  $G_{\alpha/z}$ ,  $G_{o1}$ ,  $G_{o2}$ ,  $G_q$  and  $G_{11}$  regulatory proteins. Decreases of 20 to 60% on the  $G\alpha$ -like immunoreactivity could be observed in various structures of mouse brain. In mice injected with the ODN to  $G_{i2}\alpha$  subunits the antinociceptive activity of all the opioids studied appeared greatly impaired. The analgesia evoked by opioids binding  $\mu$  opioid receptors, [D-Ala<sup>2</sup>,N-MePhe<sup>4</sup>,Gly-ol<sup>5</sup>]enkephalin (DAMGO) and morphine, appeared attenuated in mice injected with the ODN to  $G_{o1}\alpha$ . Moreover, the effects of DAMGO and morphine were also impaired after reducing the expression of  $G_{q}\alpha$  and  $G_{13}\alpha$  subunits respectively. The ODNs to  $G_{i3}\alpha$ ,  $G_{i2}\alpha$  and  $G_{11}\alpha$  subunits reduced the effects of the selective agonists of  $\delta_1$ , [D-Pen<sup>2,5</sup>]enkephalin (DPDPE) and of  $\delta_2$ -opioid receptors [D-Ala<sup>3</sup>]deltorphin. Notably, the effects of DPDPE and of [D-Ala<sup>3</sup>]deltorphin were also linked to  $G_{i1}\alpha$  and  $G_{q}\alpha$  respectively. The ODN to  $G_{i1}\alpha$  subunits lacked effect on opioid-evoked analgesia. Thus, the  $\mu$  and  $\delta$  opioid receptors regulate different classes of G transducer proteins to mediate the analgesic effect of agonists. The existence of subtypes of the  $\delta$  opioid receptor is also suggested.