CLOZAPINE AND THE NEUROPSYCHOLOGY OF SCHIZOPHRENIA

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There is some evidence that the syndromes of schizophrenia may be secondary to the specific neuropsychological deficits which have been characterised in this disease. Clozapine's (CLOZ) superior antipsychotic efficacy may lie in the amelioration of such deficits, which may not be susceptible to conventional treatment. This is an ongoing naturalistic prospective study recruiting treatment resistant inpatients who commence CLOZ or continue treatment as usual (TAU). Group membership is decided on clinical grounds, e.g. felt reasonable to await further 24 months for CLOZ, refusal of/unfit for CLOZ. Some patients have crossed over groups, acting as their own controls. Very detailed assessments take place at baseline, 6, 12 and 24 months: clinical (syndromes and motor disorder), neuropsychological (general cognition, memory, executive function) and social (social/self care abilities, behaviour problems, global rating). Neuropsychological and social function assessments are made independently of clinical ratings. Baseline assessments have not differed significantly between CLOZ and TAU groups. 6 month data (8 CLOZ, 12 TAU) and 12 month data (5 CLOZ, 8 TAU) showed significant improvements in global cognition, memory and executive function, negative symptoms and behaviour problems on clozapine: there were no improvements on any assessment with TAU. However, there was no simple correspondence between improvements in syndromes and improvements in aspects of cognition, the former appearing to precede the latter contrary to theoretical expectations. The most marked improvements were in global social function and behaviour problems. Clozapine appears to have a general 'humanising effect' rather than specific actions on a neuropsychological substrate. I will report further 6 month (14 CLOZ, 12 TAU) and 12 month findings (9 CLOZ, 10 TAU) plus preliminary 24 month data (4 CLOZ, 6 TAU).

CPT-LINKED SCHIZOPHRENIA VULNERABILITY, PSYCHOSIS PRONENESS AND FRONTAL DYSFUNCTION IN NORMAL ADOLESCENTS

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Introduction: Schizotypy, as a construct referring to liability to schizophrenia, is becoming nowadays a hot spot in schizophrenia research. Following the new strategies in the investigation of the high risk for schizophrenia condition (strategies that involve detection of schizotypic individual in the general population through a *psychometric high risk strategy*), we have studied a sample of 1498 (774 males and 724 females) normal adolescent junior highschool students randomly selected from the educational center census of Barcelona.

Methods: The main goal of this study was to examine the performance on frontal lobe tests of a group of normal adolescent subjects (Control group) and a group of subjects psychometrically defined as schizotypics (Index group) using a double criterium: 1) Continous Performance Test identical pairs version (CPT-IP, Cornblatt et al., 1988) -linked attentional deficit vulnerability and 2) a psychosis proneness measured with the Chapman's Perceptual Aberration Scale (PAS, Chapman et al., 1978) and the Social Anhedonia Scales (SAS, Chapman et al., 1976). The original sample (1498) was examined with the CPT-IP. The worst CPT-IP performers (lowest 10%, i.e. bottom decile) were selected and constitued our 'Index group' (n = 162). A group of matched (sex, age, schoolroom) subjects with normal CPT-IP performance were selected and formed the 'Control group' (n = 140). These subjects (n = 302) were then assessed with two measures of 'psychosis-proneness', the SAS and the PAS, and a frontal-lobe tests battery which included the Wisconsin Card Sorting Test (WCST), the Trail Making Test (TMT forms A and B) and a word generation test. The 10% highest and lowest PAS and SAS corers (i.e. top and bottom deciles) of the working sample (n = 302) marked the cut-off points to classificate 'low/high-PAS' and 'low/high-SAS' subjects. We hypothesized that 'schizotypic' adolescents, defined by their CPT-linked schizotypy vulnerability and by their proneness to perceptual distortions and social anhedonia, would show subtle defects in frontal lobe function compared with control subjects.

Results: Results show that Index subjects obtained higher scores on the psychosis-proneness measures (PAS and SAS), even though the difference was only statistically significant for the SAS scores. We also found that Index subjects performed worse in all the frontal-lobe tests when compared to control subjects. Most of the measures reached statistical significance. A one-way analysis of variance showed that subjects with both CPT-linked vulnerability and psychosis proneness were the worst performers when compared with subjects with only one or none of these conditions. These results suggest the existence of a subtle frontal lobe dysfunction in 'normal' adolescents that are at increased risk for schizophrenia. Our results agree with current theories that hypothesize a possible frontal-limbic dysfunction latent in the schizophrenia spectrum disorders.

COGNITIVE NEUROPSYCHOLOGY OF DELUSIONAL MISIDENTIFICATION SYNDROMES

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Introduction: Recent cognitive neuropsychological studies of the delusional misidentification syndromes (DMI) have demonstrated face recognition impairments associated with right hemisphere (RH) dysfunction. Cases of DMI have also been reported in which recognition impairments have been associated with items other than faces. We decided to determine whether these impairments in RH function extended beyond faces to another category (animals) in which high levels of within-category visual similarity exists.

Method: DMI cases, each diagnosed with paranoid schizophrenia and identified as having Fregoli syndrome were selected on the basis of earlier clinical interviews. Fregoli syndrome is characterised by the delusional belief that a familiar person has adopted a disguise, thus, whilst appearing as a different person in physical terms, the identity of the person remains unchanged. A group of age- and education-matched paranoid schizophrenic controls were selected from the same patient pool. None had experienced any reported episode of delusional misidentification. The performance of a group of age-matched nonpsychotic subjects is also reported. Pairs of computer-stored stimuli were presented to either the left (LVF) or right visual field (RVF) in a forced-choice format. The subject's task was to indicate whether they were the same (i.e. identical) or different. Exposure duration for the test stimuli was 160 ms (to control for eye-movements). Reaction time and error rates were recorded.

Results: No group showed a visual field preference for the inanimate stimuli. However, we found a LVF/RH processing advantage for the animate stimuli amongst both our set of normals and psychotic controls. The DMI-group on the other hand showed an abnormal RVF/LH preference for this class of stimuli.

Conclusions: We have shown that the DMI group are impaired with the processing of animal stimuli. This deficit was observed during the non-psychotic phase of the disorder, suggesting a sustained rather than a transitory impairment. Explanations of DMIs should

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not be confined to models of face-processing, but be extended to models of visual recognition in general.

AMISULPRIDE IN THE TREATMENT OF ACUTE EXACERBATIONS OF SUBCHRONIC OR CHRONIC SCHIZOPHRENIA: A DOSE RANGE FINDING STUDY

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Amisulpride (AMI) is an antipsychotic agent with highly selective affinity for dopamine D_2 and D_3 receptors, devoid of affinity for other neurotransmitters. In animal studies AMI preferentially binds to receptors in the limbic area. This profile suggests antipsychotic activity with a low risk of associated extrapyramidal symptoms. The short-term (4 weeks) efficacy and safety of AMI were evaluated in this study comparing four fixed doses of AMI (100, 400, 800 and 1200 mg/d) and 16 mg/d of haloperidol (H). All other AMI doses and H were compared with AMI 100 mg/d as potentially subtherapeutic dose. After a washout period of 3 to 7 days, patients fulfilling DSM III-R criteria for schizophrenia (paranoid, disorganized or undifferentiated type) could be included into the study. Efficacy was evaluated using the BPRS (main criterion), the PANSS Positive and Negative Subscales and the CGI. Safety evaluation included the UKU side effect scale, the Simpson-Angus (SAs) scale (parkinsonism), the Barnes Akathisia Scale (BAS) and the AIMS (tardive dyskinesia). A total of 319 patients (mean age 36 yrs, sd 11, mean duration of illness 10.1 yrs, sd 8.3) were included in the study. About half of the patients (46%) were pretreated with neuroleptics in the month before inclusion into the study. The mean BPRS total score (1 to 7 scoring) at inclusion was 61.2 (sd 11.4), the corresponding PANSS Positive and Negative scores were 25.9 (sd 6.0) and 27.3 (sd 8.1). 237 patients (74%) completed the study. The AMI 800 mg group had the lowest dropout rate for inefficacy (2/64 patients, $p < 0.05$ vs AMI 100 mg), whereas the H group had the highest dropout rate for safety reasons (10/64 patients, $p < 0.05$). The highest improvement (BPRS total score) was found in the AMI 400 and 800 mg groups (24.9 sd 18.4 and 26 sd 14.9, unadjusted $p < 0.05$). The corresponding response rates (CGI) were 66% and 78% respectively, ($p < 0.01$ for AMI 800). PANSS positive scores also improved significantly in the AMI 800 group (12 sd 6.9, $p < 0.05$). PANSS negative scores improved most in the AMI 400 and 800 groups (8.4 sd 7.9 and 9.6 sd 8.7) but this difference failed to reach significance. Extrapyramidal symptoms (parkinsonism) did not increase significantly in the AMI 400, 800 and 1200 mg groups compared with AMI 100, whereas increase was significantly higher in the H group ($p < 0.002$). Akathisia and tardive dyskinesia scores did not change significantly during treatment. Vital signs and biological tests showed no clinically relevant abnormalities in the different treatment groups. Overall, Amisulpride at daily doses of 400 and 800 mg proved to be highly effective on productive symptoms in acutely exacerbated schizophrenic patients with an additional effect on negative symptoms in these patients and significantly better extrapyramidal safety compared with haloperidol.

CLOZAPINE AND RISPERIDONE IN THE TREATMENT OF THERAPY-RESISTANT SCHIZOPHRENIA: A PRELIMINARY REPORT ON TWO ONGOING CLINICAL TRIALS

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Background: Clozapine proved to be effective in patients not responding to other neuroleptics. This effect has been known for years. More recently it has been shown that also Risperidone can effectively be used in these patients. We present preliminary results of two uncontrolled trials evaluating the effects of Clozapine and Risperidone on schizophrenic patients non-responding to other neuroleptic agents.

Methods: We performed two clinical trials in a parallel research design. 26 schizophrenic patients (ICD 10, mean age 46 y.) who had failed to respond to two or more different neuroleptics — each given for three weeks at least — were assigned by their individual psychiatrist to either Risperidone (n = 14) or Clozapine (n = 12). In both studies sociodemographic data were recorded, psychopathology and extrapyramidal symptoms were assessed by the same independent blind-observer in the washout period (week 0), after week 2 and after week 6 of treatment, using PANSS, BPRS, CGI, NOSIE and EPS rating scales. Statistic analysis was performed comparing rating scores between weeks 0, 2, and 6 using Students-t-test in each study separately.

Results: BPRS total score in the Clozapine Study decreased from 54.3 to 52 (−4.2%, week 2) to 50.1 (−7.7%, week 6). The corresponding score in the Risperidone Study was 52.9 (week 0), 47.9 (−9.5%, week 2) and 40.7 (−23.1%, week 6). PANSS total score in the Clozapine Study could be reduced from 84.1 to 80.3 (−4.5%, week 2) to 77 (−8.4%, week 6). Only the decrease in the positive syndrome scale was significant ($p = 0.01$). PANSS total score in the Risperidone Study was 81.2 (week 0), 72.4 (− 10.8%, week 2) and 61.0 (−24.9%, week 6). The decrease on positive syndrome scale (week 6), general psychopathology scale (week 6) and on total score of PANSS (week 2 and 6) was nearly significant ($p = 0.05$). Extrapyramidal symptom scores were remarkable low and decreased during treatment in both studies.

Conclusions: In this intermediate analysis we observed an effect of both drugs in the treatment of initially pharmaco-resistant schizophrenia which reached statistic significance in the so far small samples. However there was a difference in the magnitude of observed treatment effects favoring Risperidone. The observed differences may be due to the uncontrolled study design, unmeasured confounding risk factors, chance or a true difference between both drugs.

PSYCHOPATHOLOGY AND COGNITIVE (EXECUTIVE) DYSFUNCTION IN RELATION TO DURATION OF INITIALLY UNTREATED PSYCHOSIS IN SCHIZOPHRENIA

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While determinants of the course of schizophrenia are unclear, emerging evidence suggests that the longer psychosis proceeds unchecked before initiation of anti-psychotic therapy, the poorer may be long-term outcome. We have examined current psychopathology using the Positive and Negative Syndrome Scale (PANSS), general cognitive function using the Mini-Mental State Examination (MMSE) and executive/frontal function using the Executive Interview (EXIT) in 48 older patients with schizophrenia, many of whom were admitted in the pre-neuroleptic era. After controlling for age and for the duration and continuity of subsequent neuroleptic treatment, increasing duration of initially untreated psychosis was associated with greater severity of negative ($p < 0.005$) but not positive (NS) symptoms, and with lower scores on the MMSE ($p < 0.05$) but not with EXIT performance: duration of illness following initiation of treatment was not associated with psychopathology. Overall performance on the MMSE decreased prominently with age/duration of illness, while EXIT performance changed consid-

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