Activation of hypothalamic orexin neurons is a potential mediator of the weight gain associated with some antipsychotic drugs. Male rats display increased Fos expression in lateral hypothalamic orexin neurons following clozapine administration; however, amphetamines led to increased Fos expression in medially located orexin neurons. The rhesus monkey (Macaca mulatta) provides a model to examine the relationships between orexin neurons, weight and physical activity. Using stereology, the number of orexin-A immunoreactive neurons was quantified in 18 male (7.6-18.3kg) and 18 female (4.8-12.2kg) monkeys. In females, there was no relationship between weight and medial or lateral orexin-A neuron number. Conversely, in male monkeys, higher body weight was significantly associated with less medial orexin-A neurons ($P<0.05$), but the relationship with lateral orexin-A neurons only approached significance ($P=0.075$). Of the 36 animals in which orexin-A neurons was estimated, activity was monitored for 21 days via an Actiwatch-64 in 12 males and 12 females. Weight was negatively associated with activity in males ($P<0.05$), but not females. Comparisons of activity to orexin-A neurons revealed a significant association between higher activity levels and greater numbers of orexin-A neurons in the medial hypothalamus ($P<0.05$) but not with those in the lateral hypothalamus of males. Females showed no relationship between orexin-A neurons in either region and activity. The significant relationship between weight, activity, and medial orexin-A neurons of males, indicates that in monkeys, the medially located orexin neurons may be more influential in mediating body weight than in the rodent. (Supported by NIH Grant-P01-AG00001-29 and RR-00165).

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Neurochemical markers for aggression-related personality traits

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Background: Various biological risk factors for aggressive behaviours have been proposed, including disturbances in monoaminergic neurotransmission, endocrine axes and central nervous system (CNS) integrity.

Aims: To describe findings of correlations between markers of CNS chemical integrity, neurotransmission and hormone metabolism in relation to personality traits from forensic psychiatric investigees and normal subjects in a stress paradigm.

Method: Cerebrospinal fluid (CSF) and serum (S) samples from 46 forensic psychiatric investigees and 35 healthy subjects undergoing knee replacement surgery were analysed in relation to aggressive personality traits as rated by the Karolinska Scales of Personality, the Psychoapthy Checklist-Revised and the Temperament and Character Inventory.

Results: Aggressive traits were especially associated with increased HVA/5-HIAA ratios, indicating a deficient serotonergic tonic regulation of the monoaminergic activity, and with indices of deficient CNS integrity, such as increased CSF/S albumin ratios.

Conclusion: Neurobiological vulnerability factors are associated with aggressive behavioural and personality traits.

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Time course of emotional responses: the effects of subjective ratings of emotional intensity and voluntary supression

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Background: Emotional regulation plays a pivotal role in socialization and personal development. However, little is known about the time course of emotional responses and the interaction with the subjective assessment of emotional intensity. The aim of this project was to examine the time course of emotional responses to visual stimuli when they naturally subside and when they are cognitively suppressed.

Methods: Healthy volunteers (n=48) viewed 54 images, each lasting for 6 sec, taken from the International Affective Picture System (18 positive, 18 negative, 18 neutral). In the passive condition, subjects had to press a button to view the next image when their response had subsided. In the active condition, subjects had to press a button to view the next image when their response was successfully suppressed. After each presentation, participants rated the intensity of their response on a scale from 1 (lowest) to 9 (highest). Time to resolution (TTR) after image presentation and intensity ratings were averaged (mean±SD).

Results: TTR (seconds) for neutral images was 7.22 ± 7.91 and 4.49 ± 5.41 for passive and active condition, respectively. For positive images, 12.1 ± 9.2 and 8.66 ± 7.13 for passive and active condition, respectively. For negative images, 15.68 ± 10.14 and 11.42 ± 8.25 for passive and active condition, respectively. TTR was statistically significantly shorter ($p<0.006$) for all images during suppression. TTR in both conditions correlated positively with intensity of emotional response.

Conclusions: TTR of emotional responses to emotionally valenced images increases with intensity of the associated response and decreases with voluntary suppression.

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The effect of personality dimensions on subjective and objective measures of emotional reactivity

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Background: This study explores the contribution of personality dimensions as a source of individual variability, to electrodermal arousal, subjective ratings of intensity and time to resolution (TTR) of emotional responses to affectively valenced images.

Methods: Healthy volunteers (n=48) viewed 54 images from the International Affective Picture System equally split in positive, negative and neutral categories. Subjects pressed a button to view the next image when their response had naturally subsided (passive condition) or following voluntary suppression (active condition) and then rated the intensity of their response on a scale from 1 (lowest) to 9 (highest). The amplitude of the maximum peak of skin conductance responses (SCRs) was also measured. Personality dimensions were assessed with the Eysenck Personality Inventory (EPQ-Neuroticism, EPQ-Psychoticism and EPQ-Extraversion).

Results: Linear regression analyses were conducted to examine the effect of EPQ-P, EPQ-N and EPQ-P on TTR, intensity ratings, and maximum SCR amplitude in each experimental condition.

The emotional valence of the pictures was the strongest predictor of all 3 main outcome measures in both active and passive condition accounting for 36% of the variance for TTR, 72% for the intensity ratings and 16% for the maximum SCR amplitude. Higher EPQ-Psychoticism

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scores predicted lower intensity ratings accounting for about 10% of the variance in both conditions. EPQ-Extraversion and EPQ-Neuroticism explained 15% of the variance in TTR but in opposite directions. Higher EPQ-Neuroticism scores predicted lower SCR amplitude accounting for 8% of the variance.

Conclusions: Measures of emotional reactivity show distinct patterns depending on experimental condition and personality characteristics.

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The study of brain function in first-episode schizophrenia by functional MRI

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Background and aims: To explore the characteristics of cerebral activation during the performance of WCST in first-episode, drug-naive schizophrenic patients by functional magnetic resonance imaging,-Wisconsin Card Sorting Test (WCST) and Color Card Sorting Test (CCST).

Methods: Twenty healthy adults and twenty schizophrenic patients underwent fMRI with a 1.5T MR imager with gradient echo-EPI sequence during the performance of Wisconsin Card Sorting Test (WCST) and Color Card Sorting Test (CCST). The functional images of two groups were analyzed with analysis software. The active volume of interested brain areas and the performance of WCST were compared between healthy group and patient group. Results:(1) The performance of WCST in first-episode drug-naive schizophrenic group were significantly lower than the performance in healthy group($P<0.01$) . (2) The images subtracted the functional images of CCST from those of WCST in healthy group suggested that activations were mainly localized in the bilateral frontal lobe, especially the dorsolateral prefrontal cortex,-posterior parietal cortices and anterior cingulate gyrus.(3)The patients group showed less activations in left dorsolateral prefrontal cortex($P<0.01$), left anterior cingulated ($P<0.05$),but more activations in left posterior parietal cortices($P<0.05$).

Conclusion: The dorsolateral prefrontal cortex and anterior cingulate of first-episode schizophrenic patients are hypofunction,which maybe involved in the executive function disorder in schizophrenia. The hyperactivity of posterior parietal cortices maybe can compensate the hypofrontality in a certain extent.

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Pharmacogenetics of weight gain and obesity following clozapine treatment

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Weight gain is a major problem associated with long-term antipsychotic drug treatment. Clozapine is known to induce particularly profound weight gain. Although the mechanism of it is not clearly understood, the 5-HT2C receptor and leptin are implicated in its development. The present study examined the effects of 5-HT2C and leptin gene polymorphisms on weight change and obesity in the patients on clozapine.

107 patients (mean age 39.5±10.1 y.) meeting ICD-10 criteria for schizophrenia or schizoaffective disorder receiving clozapine took part in this study. The patient assessment included an interview, measures of weight, height, waist-hip ratio, waist circumference, body mass index (BMI, kg/m2); blood samples were taken for random blood glucose and genetic testing for 5-HT2C and leptin gene.

Central obesity was present in 102 patients as defined by increased waist circumference and obesity in 67 patients as defined by BMI>30. Type II diabetes was present in 8 patients and type I diabetes in one. In 93 patients (62M, 31F) we assessed change in BMI and weight during treatment which was 2.6±4.2kg/m2 and 7.43±12.35 kg, respectively.

There was no association between 759C/T 5-HT2C receptor and -2548A/G leptin gene polymorphisms with BMI or weight.

No association between 759C/T 5-HT2C receptor and -2548A/G leptin gene polymorphisms was found with change of BMI or waist circumference.

We found no significant association between 759C/T 5-HT2C receptor and -2548A/G leptin gene polymorphisms and changes in BMI or weight in the patients treated with clozapine.

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MEG investigation of abnormal semantic priming in schizophrenia

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Schizophrenia is associated with profound communication disorders resulting in a major social handicap. Hardy-Baylé and colleagues hypothesized that such impairments are related to a failure to process contextual integration. Previous studies based on event related potentials recordings (ERP) during semantic priming tasks have shown that schizophrenic patients have abnormal modulation of the N400 component. Supposedly, this electrical characteristic reflects an abnormal use of semantic context during word processing. However, the neural substratum underlying this pathological phenomenon remains poorly understood. To enrich knowledge inherited from ERP studies, we used magneto-encephalography (MEG) to determine the peculiarities (in anatomical and temporal terms) of the neural generators involved in semantic context integration in schizophrenia. The current study consisted in recording ERP and MEG signals during a French word-pairs lexical decision task (LDT). Subjects had to decide whether ''target words'' belonged to the lexicon or not, those words being preceded by word primes. The semantic relatedness between primes and targets varied (presence or absence) across two experimental conditions. Data obtained from a group of treated schizophrenic patients are compared to those from a healthy population. We report the preliminary results of schizophrenic subjects demonstrating that semantic priming elicits magnetic signals in the 300 to 500ms time window. Single subject's analysis of ERP and MEG profiles shows that the latter offers a different and complementary access to the brain response associated with LTD. Thus, MEG technique is suitable for investigating schizophrenic semantic priming abnormalities.

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Working memory and executive function: relation to psychiatric candidate genes

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