EV1232

F17464 a new antipsychotic with preferential D3 antagonist, 5-HT1A partial agonist properties. Neurochemical studies

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F17464 is a new dopamine receptor antagonist that recently demonstrated antipsychotic activity in a proof of concept study in schizophrenic patients under acute exacerbation. The compound has a unique profile with high affinity for hD_3 receptors (Ki = 0.17 nM) and lower affinity for hD_2L (Ki = 12.1 nM) and hD_2S (Ki = 6.5 nM). F17464 exhibits also high affinity for h5-HT_{1A} receptors (Ki = 0.16 nM). F17464 is a hD_3 antagonist (pK_B = 9.13), hD_2S very week partial agonist (pK_B = 7.87, emax 8% of DA stimulated in ERK assay) and a 5-HT_{1A} partial agonist (pEC50 = 7.99). F17464 exhibits consistent affinities for rat striatal D_2 (Ki = 4.8 nM) and for rat hippocampal 5-HT_{1A} receptors (Ki = 1.14 nM). Neurochemical studies show that F17464 ip (1 h post-dose) produces a significant dose–dependent increase in the levels of DOPAC and HVA in the frontal cortex, caudate-putamen and limbic forebrain and an increase in 3-MT levels in the latter two regions with no changes in total DA content. The effect is significant at the doses of 0.63–2.5 mg/kg ip (PK/PD data will be provided). This pattern of DA metabolite changes is similar to that described for several antipsychotic drugs in rodents and it is indicative of a cortical effect of F17464. F17464 has a very low cataleptogenic activity in rats and mice and does not induce serotoninergic signs typical of 5-HT_{1A}. F17464 is therefore a novel a D_3 preferential antipsychotic with a unique mechanism of action and receptor affinity profile and a consistent effect in neurochemistry studies in rodents.

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A novel methodology to evaluate the molecular validity of preclinical psychosis models compared to schizophrenia brain pathology

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Rodent models of schizophrenia (SCZ) are indispensable when screening for novel treatments, but quantifying their translational relevance with the underlying human pathophysiology has proved difficult. A novel systems methodology (shown in Figure 1) was developed integrating and comparing proteomic data of anterior prefrontal cortex tissue from SCZ post-mortem brains and matched controls with data obtained from four established glutamatergic rodent models, with the aim of evaluating which of these models represent SCZ most closely. Liquid chromatography coupled tandem mass spectrometry (LC-MS^E) proteomic profiling was applied comparing healthy and "disease state" in human post-mortem samples and rodent brain tissue samples. Protein-protein interaction networks were constructed from significant abundance changes and enrichment analyses enabled the identification of pathophysiological characteristics of the disorder, which were represented across all four rodent models. Subsequently, these functional domains were used for cross-species comparisons. Five functional domains such as "development and differentiation" represented across all four rodent models, were identified. It was quantified that the chronic phencyclidine (cPCP) model represented SCZ brain changes most closely for four of these functional domains, by using machine-learning techniques. This is the first study aiming to quantify which rodent model recapitulates the neuropathological features of SCZ most closely. The methodology and findings presented here support recent efforts to overcome translational hurdles of preclinical psychiatric research by associating behavioural endophenotypes with distinct biological processes.

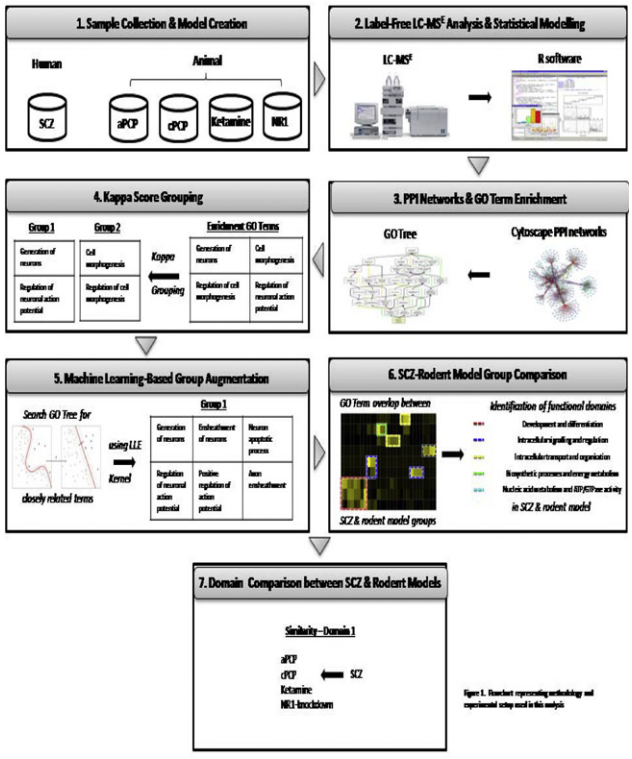

Fig. 1

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EV1234

The geometrical analysis of handwriting as a new tool to evaluate motor symptoms in psychosis

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Introduction There is growing evidence about the importance of motor symptoms in psychosis. Motor abnormalities have been observed in naive-drugs, first-episode patients. Clinical assessment of motor abnormalities normally relies upon subjective observer-based ratings. Kinematic analysis of handwriting has proved to be an objective measure of motor symptoms, but it has not been used in clinical settings.

Objectives In the present work, the geometrical analysis of handwriting patterns is proposed as a new tool to evaluate motor symptoms in psychosis.

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Method Overall, 35 healthy participants and 43 patients with psychosis from San Agustín Hospital (Linares, Spain) participed in the study. Participants were asked to write with a pen on a white paper (see patterns in the Figure 1). In order to analyze the heterogeneity of handwriting pattterns, we employed lacunarity, a nonlinear measure previously used in the analysis of biomedical images. Lacunarity measures the distribution of gap sizes in a geometrical space. A large value implies large gaps and clumping of points, whereas a small value suggests a uniform distribution with shorter gaps.
Results Lacunarity was significantly higher in handwritten patterns from patients than in controls. In addition, we found a higher heterogeneity in patients with motor symptoms in comparison with patients without motor symptoms.
Conclusions Our results suggest that analysis of handwritten patterns can be a valuable method in the evaluation of motor symptoms.

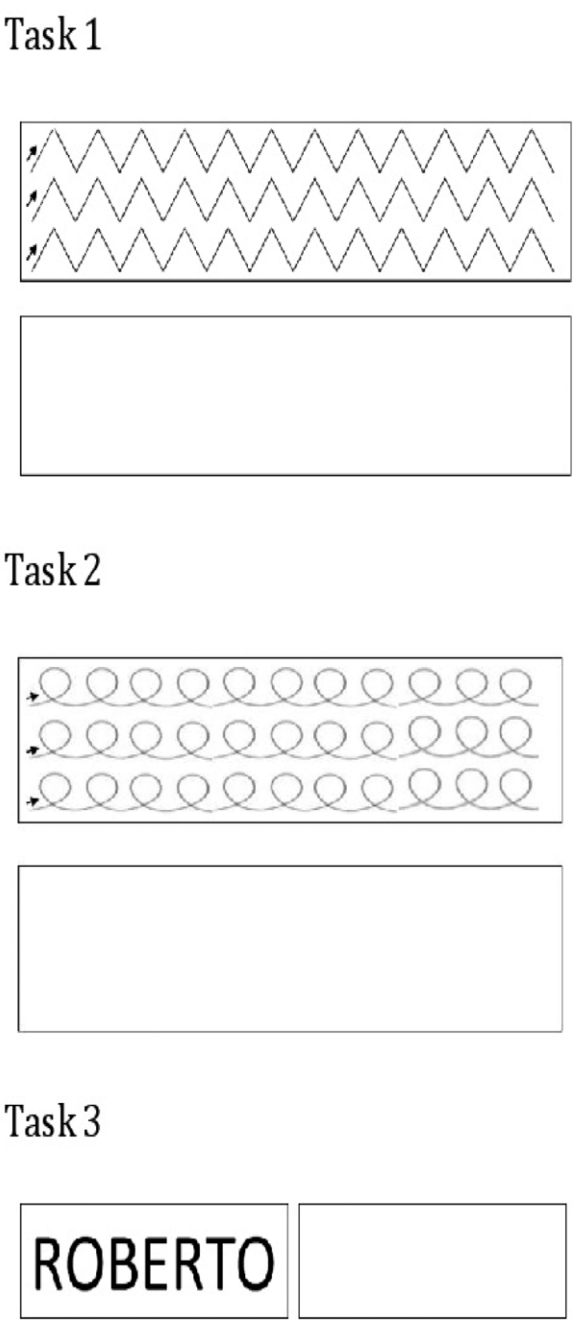

Fig. 1

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