Allegato 2 – Tematiche di ricerca e innovazione Spoke 5

1. CHARACTERIZATION OF GENETIC VARIANTS AND CLINICAL VARIABLES ASSOCIATED TO THE RISK OF SIDE EFFECTS IN PERSONS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER TREATED WITH ANTIPSYCHOTIC DRUGS

First generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) are the cornerstones in the pharmacological treatment of schizophrenia and bipolar disorder. These classes of drugs are associated to side effects with a different profile, since FGAs induce especially extrapyramidal motor symptoms and SGAs are more likely associated to metabolic side effects. Those side effects may impair the patient's compliance to treatment, increase the risk for cardiovascular unhealthy consequences, induce cognitive deficits and impair the patient's quality of life. Therefore, it would be extremely useful to identify factors that could predict the risk to develop a given side effect in order to be able to prevent it. Genetic factors could be in part responsible for the individual's vulnerability to antipsychotic (AP)-induced side effects. Genetic association studies of single nucleotide polymorphisms or genome wide association studies have been conducted to identify those genetic variants that could underlie the vulnerability to develop AP-induced side effect, but results are not conclusive. Therefore, more sophisticated genetic analyses are warranted. Furthermore, the interactions between genetic and clinical factors in the determinism of the risk of AP-induced side effects has been scantly investigated. The main objectives of this call are:

1. The characterization of genetic variants, including rare variants and *de novo* variants, associated to the risk of AP-induced side effects in persons with schizophrenia or bipolar disorder through whole exome sequencing and whole genome sequencing-long reads in both patients and their parents;
2. The characterization of clinical and demographic variables that could contribute to that risk;
3. The study of possible interactions between genetic variants and clinical variables in the determinism of the risk of AP-induced side effects

Workpackage dello Spoke 5 al quale la proposta si collega:
WORKPACKAGE 3 – Looking for genetic variants as risk factors for mood and psychotic disorders

2. GENETIC AND CLINICAL VARIABLES ASSOCIATED TO LITHIUM RESPONSE IN BIPOLAR DISORDER

Bipolar disorder (BD) is a serious, chronic psychiatric illness ranking in the top 10 causes of disability and mortality worldwide. Long term treatment with mood stabilizers is the cornerstone of the clinical management of BD. After more than 60 years, lithium remains the first-line treatment for prevention of manic and depressive episodes in BD. It appears to be on average more effective than other medications and it is also superior with respect to reducing the risk of suicide. However, lithium presents several dilemmas. First, its benefits come at a price of side effects for a proportion of patients, including risk of renal impairment after long term use as well as narrow therapeutic range and risk of adverse interactions with other medication classes. Second, lithium works in only approximately one-third of BD patients – that means that in unselected patients with BD a treatment response is less likely than non-response. There is suggestion of bimodal distribution of the degree of response with a smaller group of partial responders in between. The time to response varies greatly between patients, but on average it takes a long time to establish if the treatment is effective. This is highly relevant clinically – we have no guidelines as to how long a trial of lithium needs to be as there are no studies that would inform the clinical decision. To choose among current options, clinicians rely on a "trial-and-error" approach. As a consequence, most patients receive sequential trials of different medications. Avoiding ineffective treatments and reducing the number of sequential trials of different mood stabilizers will shorten the often-long gap between start of a treatment and satisfactory response. A biological test or easy-to-measure biomarkers able to detect patients for whom lithium would be effective could help clinicians to choose an optimal treatment. Conversely, it will help choose an alternative in those expected not to

respond to lithium. This prediction would also decrease the unnecessary exposure to potential side-effects for patients.
The main objectives of this call are:

1. The characterization of genetic variants, including rare variants, associated to response to long-term lithium treatment;
2. The study of possible interactions between genetic variants and clinical variables in the determinism of response to long-term lithium treatment;
3. The assessment of machine learning based multimodal algorithms integrating clinical and genetic factors in predicting with sufficient accuracy lithium response.

Workpackage dello Spoke 5 al quale la proposta si collega:
WORKPACKAGE 5 – Pharmacogenetics for precision medicine in mood and psychotic disorders

3. EFFECTIVENESS OF COGNITIVE TRAINING IN PERSONS WITH SCHIZOPHRENIA OR BIPOLAR DISORDER

Cognitive impairment represents one of the core features of schizophrenia and has been considered an essential characteristic of the disorder since its earliest conceptualizations. Significant cognitive impairment, expressed as a global cognitive performance that is between 1 to 2 standard deviations below the population average, affects more than 80% of diagnosed patients. Cognitive impairment is evident since the first manifestations of schizophrenia and often predates the clinical onset of the disorder. Neurocognitive domains showing significant impairment in schizophrenia are mostly attention/vigilance, speed of processing, visuospatial learning and memory, verbal learning and memory, working memory and reasoning and problem solving (also called executive functions). Cognitive impairment represents one of the most important determinants of real-world functioning in schizophrenia: more severe deficits in cognitive performance represent a strong predictor of worse outcomes in real-world interpersonal relationships, participation in community activities and work situations. Bipolar disorder (BD) is known to be associated with cognitive impairment, which persists between illness episodes, also after clinical remission from mood episodes, and contributes to functional disability. Impairment is typically found on tests of attention, working and episodic memory, processing speed and executive function, with significant group differences of medium to large effect size compared to healthy comparison groups. The pattern of non-specific cognitive deficits in BD is similar to the profile of cognitive dysfunction in schizophrenia, although generally less pronounced. However, emerging evidence points to global cognitive deficits that are as severe as in schizophrenia in 40-50% BD patients. Both schizophrenia and BD are also characterized by deficits in social cognition during the acute and remission phases, particularly in the following domains: emotional processing, Theory of Mind (ToM), attributional style, and social perception.
The main objectives of this call are:

1. To evaluate the effectiveness of cognitive training on cognition and functioning in schizophrenia and BD and the differential effect of training in the two clinical groups;
2. To evaluate how baseline cognitive functioning – together with clinical, neuroimaging and genetic variables – can predict the response to a cognitive training intervention in schizophrenia and BD, through machine learning methods;
3. To train professionals in assessing cognition and in applying cognitive remediation interventions in patients with schizophrenia and BD and measuring their effectiveness.

Workpackage dello Spoke 5 al quale la proposta si collega:
WORKPACKAGE 4 – Advanced brain imaging for mood and psychotic disorders