**Background information about some target pathologies**
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This research report is an addendum to a project proposal submitted to the MICINN. It contains the description of some of the pathologies that may be the target application for the computational methods proposed there. We gather here relevant descriptions and references provided by the participants or collaborating entities.

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The expanding availability of neuroimaging techniques with magnetic resonance imaging (MRI) and the different image acquisition sequence types, structural manifestations in the Central Nervous System (CNS) in many pathologies have been detected:

Alzheimer's Disease (AD) is the most frequent degenerative dementia in people older than 65 (7/10 demented people). Its frequency is related to the age and affects equally both genders. From the etiology point of view
there are 10% of hereditary ways linked to gene mutations that codify the prebeta-amyloid or the presenilins. The remaining cases are sporadic, but with some risk factors like the presence of the apoE allele. Pathologically, AD is defined by a presence of fibrous amyloid protein deposits in forming senile plaques and a degeneration of the neurofibrilar apparatus with neurofibrilary tangles of tau protein. From a neurochemical point of view the neurodegeneration process is mainly related to an acetylcholine deficit (the more related to mnesic symptoms neurotransmissor). Structurally, diffuse brain atrophy in MRI is observed, more typically in the medial zone of the temporal lobe.

Myotonic Dystrophy of type 1 (DM1), is a slowly progressive myopathy characterized by varying multi-systemic involvement, affecting skeletal and smooth muscle, the heart (arrythmia, conduction defects), the endocrine system (hyperinsulemia), eyes (cataracts), also presents cognitive, immunological alterations and other symptoms. DM1 is transmitted in a autosomal dominant manner and it is due to an unstable genetic mutation, where the number of (CTG)n repeats that, in normal subject it varies from 5 to 35, however in patients it occurs from 50 and more than 2500. The clinic fenotype correlates with the (CTG)n repeats number being the most serious cases the ones related to more number of repetitions. There is instability in the intergenerational transmission of the triplet that varies according to gender; expansion size grows from parents to sons (phenomenon of clinic anticipation: earlier manifestation and more serious symptoms in the case of the sons). This phenomenon varies according to the affected progenitor's gender, being the most serious in case of maternal heritage. MRI studies have found cortical atrophy in DM1, ventricular dilation and lesions in white matter (WM).

Multiple Sclerosis (MS) is an acquired disease produced by an aggression of autoimmune origin against the myelin sheaths. The reason of this aggression is unknown although there is genetic predisposition. MS affects between 50 to 100 patients over 100,000 inhabitants with a proportion women/men of 2:1 and with a gradient from north to south (it is more frequent in warm latitudes than in the tropics). Clinically, MS attends mainly with characterized appearances of a generally temporary dysfunction of some part of the CNS depending on the localization of the inflammatory phenomenon. After a time period, the repair mechanisms act and a complete or incomplete clinical improvement occurs. After some time, the CNS regenerative capacity is exhausted and the lesions start to leave scars. Besides this pattern (remitting-relapsing) there are types that evolve in a progressive manner without lesions and other benign types. In MRI, WM lesions are observed particularly in periventricular regions, nerves and optic chiasm, brainstem, cerebellar pedancle and spinal cord.

This three diseases have very different origin, manifestations and etiologies, but they share sub-cortical lesions in MRI that affect WM. While in MS these lesions are a characteristic feature and part of diagnostic criteria and evolution, in DM1, lesions usually are confluent and have the aspect of leukoencephalopathy in a certain percentage of the patients. In AD, some

patients show sub-cortical lesions of uncertain meaning that some times make a differential diagnostic with mixed degenerative-vascular very difficult.

**Psychotic disorders division McLean Hospital of the Harvard University (provided by Ann K. Shinn)**

Schizophrenia, Bipolar Disorder and auditory hallucinations

In the 19th century, German psychiatrist Emil Kraepelin (1856-1926) described schizophrenia (SZ) as a functional psychosis marked by progressively deteriorating mental function, to be distinguished from the relapsing and remitting psychosis of bipolar disorder (BP)1. The current version of the Diagnostic and Statistical Manual of Mental Illness (DSM-IV-TR)2 reflects this traditional dichotomous categorization of psychotic illness into schizophrenic and affective psychoses, and is the present standard for how patients are classified in psychiatric research and clinical practice. While the use of a categorical system has significantly improved diagnostic reliability, the validity of such diagnostic constructs has been the source of significant debate. The DSM-IV differentiates between SZ and BP primarily on the basis of course outcome and whether psychosis is the core feature of illness or secondary to a primary disturbance in mood. However, there is no clear clinical boundary between the two disorders. SZ and BP share a significant overlap in psychopathology, and in an acute psychotic episode, SZ and BP patients can appear virtually indistinguishable from one another.

In line with clinical observation, a growing body of epidemiological, genetic, and neuroscience research suggests that SZ and BP may not be biologically discrete disease entities with distinct pathogenesis, but rather overlapping syndromes on a psychosis continuum. In one of the largest population-based studies to date (over 9 million individuals identified in Sweden's multi-generation national registry), Lichtenstein et found that first-degree relatives of patients with SZ and BP were at increased risk of either of these disorders, suggesting that SZ and BP share, in part, a common genetic cause. Such evidence challenges the dichotomous Kraepelinian nosology that exists in the DSM-IV, and suggests that research should focus on dimensional measures of psychopathology, some of which traverse diagnostic categories. Such a symptom-based approach may reduce the heterogeneity that characterizes patient samples defined according to the DSM-IV, and thus improve signal detection in biological psychiatry research. More importantly, a dimensional approach may ultimately lead to improved pathophysiology-based treatments and greater public health impact. The goals of the National Institute of Mental Health (NIMH) are in accord with these objectives; in July 2010, the NIMH announced the launching of the Research Domain Criteria project, designed to create a framework for pathophysiology research that can yield classification based on biological evidence and clinical observation, with the goal of improving clinical outcomes.

Auditory hallucinations (AH), or the experience of auditory perceptions in the absence of external stimuli, constitute one of the cardinal features of SZ and other psychotic disorders. Though hallucinations are most commonly associated with SZ, occurring in an estimated 60-70% of SZ patients, hallucinations are also prevalent in mood disorders, occurring in 11-23% of BP patients and in 6% of unipolar depressed patients. While some patients have only elementary AH, for example hearing simple tones, AH in SZ are more characteristically experienced as voices that say the patients' own thoughts out loud, give a running commentary on the patient's thoughts or actions, or converse with each other12. AH can be severely incapacitating, as many patients experience such voices as real, intrusive, and distressing. Though the experience of AH can vary from person to person, AH are a symptom dimension that is common across diagnostic

categories, that many patients have descriptive access to, and that can be quantitatively measured through patient self-report. Combining systematic clinical characterization of AH with advanced neuroimaging techniques has the potential to yield important insights into the neural circuitry underlying the symptom dimension of AH. Such knowledge is critical to developing more targeted prevention strategies and interventions to patients who suffer from this clinically disabling phenomenon.

Attempts to identify the neurobiological processes underlying AH have produced no single pathophysiological mechanism. Nonetheless, at the group level, one of the most consistent findings has been the demonstration of volume reductions of the superior temporal gyrus (STG) in patients with SZ who have AH. In many of these studies, AH severity was inversely correlated with left STG volume. Several other brain regions, in addition to the STG, have been associated with AH. PET studies have shown AH to be associated with increased regional cerebral blood flow in the medial temporal lobe, anterior cingulate cortex, and Broca's language area. Deeper brain structures, including thalamus, parahippocampal gyrus, ventral striatum, and orbitofrontal cortex also showed increased regional cerebral blood flow during AH, measured by button press in the PET scanner. A recently published coordinate-based meta-analysis of cortical activations during the experience of auditory verbal hallucinations in schizophrenia, based on eight functional MRI and two PET studies, showed significantly increased activation likelihoods in five clusters distributed in temporal, parietal, frontal, and subcortical sites. The largest activations were located in Broca's area, left precentral gyrus, the bilateral anterior insula, frontal operculum, left middle and superior temporal gyri, left hippocampus and parahippocampal gyrus, and inferior parietal lobule. This body of literature suggests that brain abnormalities underlying AH are not confined to a single loci, but involve distributed networks.

The "dysconnectivity" hypothesis of SZ proposes that schizophrenia is due to abnormal functional integration of brain processes. This concept was initially proposed by Karl Wernicke (1848-1905), who postulated that psychosis arises from abnormal conduction between different areas of the cortex, and by Eugen Bleuler (1857-1939), who attributed SZ to the splitting off of different mental domains. The hypothesis suggests that SZ arises from abnormal interactions within spatially distributed neural networks. Indeed, functional MRI studies have suggested that there is abnormal functional connectivity between the temporal cortex and other brain regions in patients with AH. In a study by Lawrie et al, SZ patients underwent fMRI scanning during a sentence completion task known to activate frontal and temporal regions. While both groups showed activations of the left STG and bilateral dorsolateral prefrontal cortex, patients with SZ showed reduced coupling in the activity of these two brain regions, as measured by a correlation coefficient that was inversely associated with AH severity. In a similar paradigm, Mechelli et al used fMRI and dynamic causal modeling to show impaired connectivity between the left STG and anterior cingulate cortex (ACC) in SZ patients with AH. During scanning, subjects were asked to indicate whether the playback of a prerecorded voice was their own or alien. In contrast to healthy controls and patients without AH, SZ patients with AH showed decreased coupling of activity between the left STG and the ACC when the source of the voice was alien, and increased connectivity in these two brain regions when the speech was self-generated.

In the past decade, resting state functional MRI (rsfMRI) has emerged as an important tool for investigating functional connectivity within large-scale brain networks. Low frequency (<0.1 Hz) spontaneous fluctuations in neuronal activity take place continually in the human brain, even in the absence of specific tasks or stimuli and under anesthesia, suggesting that the activity reflects an intrinsic property of functional brain organization. These low frequency oscillations can be measured via the blood oxygen level dependent (BOLD) signal in fMRI. Because functionally related brain regions show temporal coherence in these oscillations, measuring the strength of correlations between brain regions can provide a direct measure of functional connectivity within a network. Though there has been a dramatic explosion in the number of studies using rsfMRI to

study SZ, fewer investigators have applied rsfMRI specifically to the study of AH. Some found that patients with AH had reduced interhemispheric connectivity in primary and secondary auditory cortices when compared with non-AH patients and healthy controls. Others found that SZ patients had reduced functional connectivity between the left temporoparietal junction and right Broca's homologue compared to healthy controls.

## Interacción genotipo-fenotipo mediante estudios DTI

Diferenciar los cambios neurobiológicos que suceden durante el envejecimiento normal y las enfermedades neurodegerativas permite establecer un diagnóstico diferencial. La sustancia blanca es esencial para el funcionamiento cerebral. Su desarrollo es _heterocronológico_ (Bartzokis 2004) y algunos autores encuentran un patrón curvilíneo de su volumen a lo largo de la vida (Salat et al. 2005). Se estima que con la edad se produce una disminución del 15-17% de pérdida de sustancia blanca en hemisferios cerebrales, con un 27% de reducción concomitante de longitud de las fibras nerviosas (Tang et al. 1997). Un estudio en población Danesa mostró un descenso del 10% por década del total de longitud y un 45% a lo largo de la vida (Marner et al. 2003).
Los oligodendrocitos, células productoras de mielina, son las células más vulnerables del cerebro y su vulnerabilidad aumenta con el envejecimiento, aquellos que se diferencian en edades más tardías del desarrollo tienen propiedades lípidicas diferentes y producen una mielina más susceptible a la lesión. Son células marcadamente heterogéneas en función del momento en que a lo largo del desarrollo del cerebro se diferencian en células productoras de mielina(Power et al. 2002). Las alteraciones de la sustancia blanca cerebral del anciano observadas en neuroimagen se denominaron leucoaraiosis para indicar disminución de la densidad de representación de la sustancia blanca en neuroimagen .
Su heterogeneidad patológica variabilidad regional y cuantitativa dificultan el establecimiento de su significado clínico y puede explicar la falta de consenso en los resultados de correlación clínica y anatómica. Técnicas recientes como el tensor de difusión (DTI) son herramientas que cuantifican alteraciones estructurales de los tejidos y permiten medir la anisotropía fraccional (FA) lo que resulta particularmente útil para valorar la integridad de los tractos de sustancia blanca y los circuitos de conexión entre diferentes regiones. Los aumentos de anisotropía se han correlacionado con marcadores de mielinizacion.(Hinman and Abraham 2007)
En la EA aunque los estudios sobre su patogénesis se han centrado principalmente en el papel de los depósitos proteínicos, el estudio de la sustancia blanca en su fisiopatología está adquiriendo un papel preponderante. La neurodegeneración de la EA no es global, evoluciona mostrando un patrón regional de disfunción y degeneración neuronal característica, que algunos autores encuentran pueda ser inverso al patrón de mielinización (Bartzokis 2004). Mediante técnicas sensibles a la mielina como el DTI se ha constatado que la alteración de la mielina se presenta en pacientes con EA sin evidencia de infartos , degeneración walleriana o angiopatía amiloide, y esos déficits de la SB se han observado en estadios precoces o preclínicos de la enfermedad. El DTI en la EA ha mostrado utilidad en la monitorización de la enfermedad el diagnóstico diferencial entre el DCL y envejecimiento normal (Wang et al. 2009), y entre la EA y la demencia vascular (Zarei et al. 2009).
La integridad de la sustancia blanca resulta clave también en la fisiopatología del TB. Los hallazgos estructurales de esta patología, que algunos autores opinan comparte mecanismos fisiopatologicos con la EA , no son del todo concluyentes por la información contradictoria que en ocasiones generan, sin embargo el hallazgo de LSB es el hallazgo de neuroimagen (Langan and McDonald 2009) más consistente independientemente de la edad. Estas lesiones al igual que en la EA se han asociado a patología vascular, sin embargo su presencia en edades más precoces hace pensar que otros factores puedan participar en su etiología. Mediante estudios de DTI se han encontrado recientemente asociación entres genes relacionados con la mielina y la disminución de densidad y pérdida de la integridad de la SB.
Algunos autores han estudiado la mielinización del sistema nervioso periférico(Lemke 1996) encontrando que isoformas específicas del gen (Nrg-1), se une al receptor ErbB tyrosin Kinasa expresado en las células de Schwann y sirve como inductor para desencadenar la mielinización (Lemke 2006).
Recientemente se han observado acúmulo de NRG1 en las placas neuríticas en asociación con

neuritas distróficas y microglia y se han encontrado niveles de NRG1 en el LCR de pacientes con EA (Pankonin et al. 2009). Algunos resultados sugieren que la NRG1 juega un papel creciente en el riesgo para desarrollar síntomas positivos en la EA de inicio tardío (Go et al. 2005).

Un considerable número de estudios han investigado el rol de la NRG1 en el TB como gen de susceptibilidad para desarrollar psicosis (Georgieva et al. 2008). La mayoría de estos estudios han analizado muestras combinadas de pacientes con TB y esquizofrenia (Green et al. 2005) (Thomson et al. 2007), pero hasta el momento ninguno ha estudiado una muestra combinada de pacientes con EA y TB. Teniendo en cuenta el rol de la NRG1 en la mielinización y su aparente determinación en las anomalías de la sustancia blanca en la psicosis, analizaremos mediante el tensor de difusión (DTI) los efectos de la NRG1 en la densidad e integridad de la sustancia blanca en el TB y en la EA.

Por lo anteriormente expuesto podría ser útil la utilización de técnicas de neuroimagen que permitan comparar los hallazgos de neuroimagen de estas enfermedades que con baja frecuencia son comparadas

**Alzheimer's Disease findings in MRI**

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**Multiple Sclerosis findinds in MRI**

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