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Functional Magnetic Resonance Imaging and Schizophrenia as Disconnection Disorder

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Abstract: Functional magnetic resonance imaging (fMRI) today acts as the basis for neuroimaging in cognitive neuroscience. Advances in scanner technology, image acquisition, experimental design, and analysis methods collectively push fMRI much ahead. The fMRI allows seeing activity in the brain in relation to the performance of particular behaviours as well as it measures change in blood flow related to neural activity in the brain. It produces a steady increase in the amount of research on cognitive behaviour. One of the major clinical applications of fMRI is in the diagnosis of Schizophrenia. Because of its close ties to neuroscience, fMRI has been widely used since its invention to investigate the neural basis of mental illness. Most of the major illnesses, e.g. schizophrenia and major depression, appear to represent disordered neural systems widely distributed in the brain. FMRI provides a means to assess the neurobiological theory that schizophrenia is caused by abnormal frontal–temporal lobe connections. In this paper we provide a review on functional Magnetic Resonance Imaging, the analysis of fMRI data, from the initial acquisition of the raw data to its use in locating brain activity, Methods, Tools Techniques used, their advantages, Disadvantages making inference about brain connectivity and predictions about psychological or disease states.

Keywords: MRI, FMRI, BOLD, SPM, Schizophrenia.

I. INTRODUCTION

A. From MRI to FMRI:

Magnetic resonance imaging (MRI) is the most important imaging technique since the introduction of X-rays by Conrad Rontgen in 1895. Since its introduction in the clinic in the 1980s, has assumed a role of unparalleled importance in diagnostic medicine and more recently in basic research.

In medicine, MRI is primarily used to produce structural images of organs, including the central nervous system, but it can also provide information on the physicochemical state of issues, their vascularization, and perfusion. Although all of these capacities have long been widely appreciated, it was the emergence of functional MRI (fMRI)—a technique for measuring haemodynamic changes after enhanced neural activity—in the early 1990s that had a real impact on basic cognitive neuroscience research. The principal advantages of fMRI lie in its noninvasive nature, ever-increasing availability, relatively high spatiotemporal resolution, and its capacity to demonstrate the entire network of brain areas engaged when subjects undertake particular tasks [1].

Advantages of fMRI also include:

a. High spatial resolution (1-4 mm) in-plane resolution)
b. High temporal resolution (0.1 – 1 s)
c. Noninvasive, easily repeatable technique with minimal preparation for the patient
d. Can obtain both functional and anatomical images in the same study session
e. Can be performed using most clinical scanners without adding significant costs.

Disadvantages include:

a. Like all haemodynamic-based modalities, it measures a surrogate signal whose spatial specificity and temporal response are subject to both physical and biological constraints.
b. Data obtained is noisy and not real world environment.
c. It is unsuitable for claustrophobics
d. It is also unsuitable for patients with implanted metal or pacemakers.

Functional magnetic resonance imaging (fMRI) can be used to identify regions of the brain that are associated with certain perceptual, cognitive, emotional and behavioral functions such as sensorimotor, language, and memory. Although several MRI techniques have been developed for imaging functions of the brain, such as arterial spin label (ASL), contrast agent enhanced imaging and magnetic resonance spectroscopic imaging (MRSI), the most commonly used technique is based on blood oxygenation level dependent (BOLD) imaging. BOLD imaging takes advantage of an endogenous paramagnetic contrast agent, deoxyhemoglobin, to detect MRI signal changes related to a change of deoxyhemoglobin concentration in the blood.

The BOLD signal is sensitive to local changes of blood flow and to oxygen saturation in the microvasculature, both of which are coupled to local neuronal activity.

In other words, an increase in neuronal activity is associated with a transient increase in local blood flow, and it is this increase that is measured with fMRI. A statistical comparison of images obtained during an activated condition with images obtained during a control condition can be used to reveal the activated brain regions that are specific to a particular mental task [2].

The coupling of neuronal activity to alterations in the vascular system is the basis for a number of functional imaging methods currently used in studying brain function, including positron emission tomography (PET), single photon emission computed tomography (SPECT), optical imaging and fMRI.

FMRI methods are based on two technical advances in MRI which includes: First, the emergence of fast imaging techniques, as represented by echo planar imaging (EPI) at high field (1.5 T), second, allows a set of complete two-dimensional brain images to be acquired with a single radio frequency excitation. The commonly used single-shot EPI method is capable of very fast acquisition (< 100ms/image) of multi-slice images. For example, it allows the entire brain to be covered by 28 slices, each with a slice thickness of 5 mm, in less than 3 seconds [2]. The introduction of EPI led to initial studies of the dynamic changes in cerebral blood volume using exogenous paramagnetic contrast agents, and was thus the key technical development leading to the first functional MR images of brain activity. It also led to other fast imaging methods, such as the spiral imaging method [2].

Functional MRI (fMRI) utilizing the blood oxygenation level dependent (BOLD) contrast has become an important research and clinical tool to study the normal and diseased human brain. The blood-oxygen-level-dependent (BOLD) contrast mechanism is presently the basis of human neuroimaging. The method of using endogenous contrast agents was developed which includes:

a) Contrast mechanism based on concept of altering the longitudinal proton magnetization of inflowing blood to create imaging contrast between 'tagged' protons of inflow blood (the tracer) and stationary protons of the tissue is such that thus measuring;
b) Contrast mechanism was based on the observation of local changes in the magnetic susceptibility induced by changes in the deoxyhemoglobin content of the blood, i.e. Blood Oxygen Level Dependent (BOLD) contrast.

BOLD imaging is based on the fact that deoxyhemoglobin, which is a paramagnetic molecule, induces a small local field inhomogeneity in the magnetic field of the MR scanner. As deoxyhemoglobin is confined to red blood cells, it acts as an endogenous paramagnetic contrast agent in the blood, which is modulated by variations in oxygen supply (blood flow) and oxygen consumption (tissue metabolism). The presence of deoxyhemoglobin causes a difference in the local magnetic field susceptibility between blood and surrounding tissue, which results in a T2* effect, that is a small signal drop. Consequently, a reduction in the deoxyhemoglobin concentration will produce a small signal increase. Thus, the activation induced BOLD changes can described by a somewhat simplified model. Neuronal activity causes an increase in both blood flow and oxygenation, thereby decreasing the deoxyhemoglobin concentration, which leads to a small, but measurable, MR signal increase. It is the combination of endogenous contrast and rapid imaging technology that makes it possible to detect the activation-induced MR changes [2].

It is useful to think of fMRI as being comprised of four interacting, co-evolving parts: hardware, methodology, signal interpretability, and applications. Each drives and feeds off advancements of the others. Hardware includes the primary magnet, shim coils, radiofrequency coils, receivers, and subject interface devices. Methodology includes pulse sequences, post processing, multi-modal integration techniques, and paradigm designs. Signal interpretability includes advancements in understanding the relationship between underlying neuronal activity and BOLD. Applications include not only those directed at understanding brain organization but also towards complementing clinical diagnoses, characterizing neurological and psychiatric disorders, and even towards providing therapy. Other non-medical applications include behavior prediction, lie detection, and brain–computer interfaces [3].

The data acquisition and reconstruction techniques provide the means for obtaining a static image of the brain. However, changes in brain hemodynamics in response to neuronal activity impact the local intensity of the MR signal. Therefore, a sequence of properly acquired brain images allows one to study changes in brain function over time. An fMRI study consists of a series of brain volumes collected in quick succession.

The rest of this paper is organized as follows. Section 1 is devoted to a detailed description of schizophrenia. Section 2 describes the methodologies used so far. In Section 3, the process of data acquisition is given. In Section 4 Feature extraction process is presented. Section 5 describes how to pre-process FMRI data. In Section 6 Analysis of FMRI data is presented. Conclusions are presented in Section 7.

B. Schizophrenia: A Brain Disorder:

Schizophrenia has often been conceived as a disorder of connectivity between components of large-scale brain networks [4]. It is a pervasive and complex neuropsychiatric disorder with prominent deficits in social cognition [5].Its symptoms can be conceptualized in terms of a breakdown of a balance between: 1) Activating, retrieving, and matching stored representations to incoming information (semantic memory-based processing) and 2) Fully integrating activated semantic representations with one another and with other types of representations to form a gestalt representation of meaning (semantic integration) [6].

It is generally accepted that, schizophrenia is associated with neuronal deficits; it has not been possible to explain the complex features of the disorder on the basis of specific, localized, structural or functional abnormalities. This has led to the suggestion that the basis of the illness could lie in abnormal interactions, or dis-connectivity, between a distributed networks of brain regions. In neuroimaging, functional connectivity has been defined as cross correlations over time between spatially remote brain regions [7].

Although there is considerable evidence that patients with schizophrenia fail to activate the dorsolateral prefrontal cortex (DLPFC) to the degree seen in normal comparison subjects when performing working memory or executive tasks, hypofrontality may be coupled with relatively increased activity in other brain regions. However, most imaging studies of working memory in schizophrenia have focused on DLPFC activity. The goal of this work is to review functional neuroimaging studies that contrasted patients with schizophrenia and healthy comparison subjects. Dysregulation of dorsolateral prefrontal cortex (DLPFC) is thought to be central to the neurophysiology of schizophrenia. The link between DLPFC dysfunction and disrupted working memory is a prominent feature of leading cognitive neuroscience models of schizophrenia, which propose that working memory disturbances disrupt guidance of ongoing behavior and lead to the cognitive fractionation and psychiatric symptoms characteristic of schizophrenia [8].

Working memory (WM) and prefrontal cortical function are impaired in schizophrenia and it is widely believed that an abnormality of the prefrontal cortex (PFC) contributes to this deficit. Functional neuroimaging studies of WM have demonstrated altered regional cerebral blood flow, glucose

utilization, and blood oxygen level dependent (BOLD) signal in the PFC in schizophrenia. Prefrontal cortex (PFC) covers the most anterior portion of the frontal lobes. It sub serves executive functions such as working memory, information processing, behavioral organization, and attention. Converging evidence suggests structural and functional abnormalities of the PFC in schizophrenia [8].

One of the most disconcerting sensations encountered by patients with schizophrenia is the feeling that their actions and personal states are no longer under their own control. Symptoms such as auditory hallucinations, thought insertion, thought broadcasting and the influence of others on the patient's thoughts, actions or emotions are very frequent in schizophrenia [9].

A person with schizophrenia typically experiences changes in behavior and perception, and disordered thinking that can distort their sense of reality. This is referred to as psychosis. Schizophrenia is a mental illness with much stigma and misinformation associated with it. This often increases the distress to the person and his/her family.

The onset of illness may be rapid, with acute symptoms developing over several weeks, or it may be slow, developing over months or even years. During onset, the person often withdraws from others, gets depressed and anxious, and develops unusual ideas or extreme fears. Noticing these early signs is important for early access to treatment. Early recognition and effective early treatment is vital to the future wellbeing of people with schizophrenia.

C. Symptoms of Schizophrenia:

The symptoms of schizophrenia fall into three broad categories: positive symptoms, negative symptoms, and cognitive symptoms [10-11].

- ***a. Positive Symptoms:*** Positive symptoms are psychotic behaviors not seen in healthy people. People with positive symptoms often "lose touch" with reality. These symptoms can come and go. Sometimes they are severe and at other times hardly noticeable, depending on whether the individual is receiving treatment. The positive symptoms of schizophrenia include:
  - ***a) Delusions:*** False beliefs of persecution, guilt or grandeur, or being under outside control. People with schizophrenia may describe plots against them or think they have special gifts and powers. Sometimes they withdraw from people or hide to avoid imagined persecution.
  - ***b) Hallucinations:*** Most commonly involve hearing voices. Other less common experiences can include seeing, feeling, tasting or smelling things that to the person are very real, but that are not actually there.
  - ***c) Thought Disorder:*** Here speech may be difficult to follow with no logical connection. Thoughts and speech may be jumbled and disjointed.
  - ***d) Movement Disorder:*** It may appear as agitated body movements. A person with a movement disorder may repeat certain motions over and over. In the other extreme, a person may become catatonic. Catatonia is a state in which a person does not move and does not respond to others. Catatonia is rare today, but it was more common when treatment for schizophrenia was not available.
- ***b. Negative Symptoms:*** Negative symptoms are associated with disruptions to normal emotions and behaviors. These symptoms are harder to recognize as part of the disorder and can be mistaken for depression or other conditions. Negative symptoms include the following:
  - ***a) Lack of Drive:*** Here the ability to engage in everyday activities, such as washing and cooking, is lost. This lack of drive, motivation and initiative is part of the illness, and is not laziness, Lack of pleasure in everyday life, Lack of ability to begin and sustain planned activities.
  - ***b) Thinking Difficulties:*** A person's concentration, memory, and ability to plan and organize may be affected. This makes it more difficult to reason, communicate, and complete daily tasks.
  - ***c) Blunted Expression of Emotions:*** Here the ability to express emotion is greatly reduced. This is often accompanied by an inappropriate response to happy or sad occasions.
  - ***d) Social Withdrawal:*** This may be caused by a number of factors including the fear that someone is going to harm them, or a fear of interacting with other people because of a loss of social skills.
  - ***e) Lack of Insight:*** Because of some experiences, such as delusions and hallucinations, are so real, it is common for people with schizophrenia to be unaware that they are ill. This can be very distressing for family and carriers. Lack of awareness can be a reason that people with schizophrenia refuse to accept treatment that could be helpful. The unwanted side-effects of some medications can also contribute to treatment refusal.
  - ***f) Speaking Little, Even when Forced to Interact:*** People with negative symptoms need help with everyday tasks. They often neglect basic personal hygiene. This may make them seem lazy or unwilling to help themselves, but the problems are symptoms caused by the schizophrenia.
  - ***g) Flat Affect:*** A person's face does not move or he or she talks in a dull or monotonous voice.
- ***c. Cognitive Symptoms:*** Cognitive symptoms are subtle. Like negative symptoms, cognitive symptoms may be difficult to recognize as part of the disorder. Often, they are detected only when other tests are performed. Cognitive symptoms include the following:
  - ***a) Poor Executive Functioning:*** The ability to understand information and use it to make decisions.
  - ***b) Trouble Focusing or Paying Attention.***
  - ***c) Problems with Working Memory:*** The ability to use information immediately after learning it. Cognitive symptoms often make it hard to lead a normal life and earn a living. They can cause great emotional distress.

D. Causes of Schizophrenia:

Experts think that the schizophrenia is caused by several factors [10-11].

- ***a. Genes and Environment Factors:*** Scientists have long known that schizophrenia runs in families. The illness occurs in 1 percent of the general population, but it occurs in 10 percent of people who have a first-degree relative with the disorder, such as a parent, brother, or sister. People who have second-degree relatives (aunts, uncles, grandparents, or cousins) with the disease also develop schizophrenia more often than the general population. The risk is highest for an identical twin of a

person with schizophrenia. He or she has a 40 to 65 percent chance of developing the disorder.

Other recent studies suggest that schizophrenia may result in part when a certain gene that is key to making important brain chemicals malfunctions. This problem may affect the part of the brain involved in developing higher functioning skills. Research into this gene is ongoing, so it is not yet possible to use the genetic information to predict who will develop the disease.

In addition, it probably takes more than genes to cause the disorder. Scientists think interactions between genes and the environment are necessary for schizophrenia to develop. Many environmental factors may be involved, such as exposure to viruses or malnutrition before birth, problems during birth, and other not yet known psychosocial factors.

b. Different Brain Chemistry and Structure: Scientists think that an imbalance in the complex, interrelated chemical reactions of the brain involving the neurotransmitters dopamine and glutamate, and possibly others, plays a role in schizophrenia. Neurotransmitters are substances that allow brain cells to communicate with each other. Scientists are learning more about brain chemistry and its link to schizophrenia.

Also, in small ways the brains of people with schizophrenia look different than those of healthy people. For example, fluid-filled cavities at the center of the brain, called ventricles, are larger in some people with schizophrenia. The brains of people with the illness also tend to have less gray matter, and some areas of the brain may have less or more activity.

Studies of brain tissue after death also have revealed differences in the brains of people with schizophrenia. Scientists found small changes in the distribution or characteristics of brain cells that likely occurred before birth. Some experts think problems during brain development before birth may lead to faulty connections. The problem may not show up in a person until puberty. The brain undergoes major changes during puberty, and these changes could trigger psychotic symptoms. Scientists have learned a lot about schizophrenia, but more research is needed to help explain how it develops.

d. Family Relationships: No evidence has been found to support the suggestion that family relationships cause the illness. However, some people with schizophrenia are sensitive to any family tension, which for them may be associated with recurrent episodes.

e. Stress: It is well recognized that stressful incidents often precede the onset of schizophrenia. These may act as precipitating events in vulnerable people. People with schizophrenia often become anxious, irritable and unable to concentrate before any acute symptoms are evident. This can cause problems with work or study and relationships to deteriorate. Often these factors are then blamed for the onset of the illness when, in fact, the illness itself has caused the stressful event. It is not, therefore, always clear whether stress is a cause or a result of schizophrenia.

f. Alcohol and Other Drug Use: Harmful alcohol and other drug use, particularly cannabis and amphetamine use, may trigger psychosis in people who are vulnerable to developing schizophrenia. While substance use does not cause schizophrenia, it is strongly related to relapse.

E. Treatment for Schizophrenia:

Because the causes of schizophrenia are still unknown, treatments focus on eliminating the symptoms of the disease. Treatments include antipsychotic medications and various psychosocial treatments [11].

F. The Role of Functional Imaging in the Study of Schizophrenia:

Understanding the cognitive pathology of schizophrenia is central to understanding the disorder. Functional imaging provides a means to study the neural basis of cognition directly, and assess the abnormal neural circuitry underpinning cognitive dysfunction. It is therefore an ideal tool to characterize a disorder where functional deficits are paramount. It has long been suspected that schizophrenia is associated with abnormal neuronal activity.

Computed tomography (CT) highlighted the importance of ventricular enlargement, and structural magnetic resonance imaging demonstrated loss of temporal lobe volume. A more recent meta-analysis by Wright et al. found consistent support for both ventricular enlargement and loss of temporal lobe matter (particularly the amygdala, hippocampus and Para hippocampal) in the brains of schizophrenic patients, and additionally reported reduced mean cerebral volume in schizophrenia. Functional neuroimaging provides a means to assess impaired functional neuro anatomy and is thus a crucial advance in the study of schizophrenia [12].

G. Subjects Selection Criteria:

FMRI experiments conducted to understand psychiatric illness among patients and normal subjects. Review provides the information regarding subjects that, both, healthy (nonpsychotic) and people with chronic schizophrenia were recruited and diagnosed according to standard operational criteria in the Diagnostic and Statistical Manual of Mental Disorders IV (American Psychiatric Association, 2000). DSM-IV* criteria for the diagnosis of schizophrenia include: i) The presence of two or more characteristic symptoms during the active /acute phase (e.g. delusions and hallucinations), ii) Evidence of social or occupational dysfunction, iii) Continuous signs of disturbance for at least six months, iv) Exclusion of schizoaffective/mood disorders, v) Exclusion of cause by a substance or a medical condition, vi) If there is also a history of pervasive developmental disorder, schizophrenia can only be diagnosed if prominent delusions or hallucinations are present for at least a month[12]. The two groups were matched against different factors e.g. age, Symptom severity scores were measured using the Positive and Negative Syndrome Scale (PANSS) scale (Kay, S., Fiszbein, A., & Opler, L., 1987). All patients were receiving antipsychotic drugs, and four were receiving additional psychotropic medication. To mitigate acute drug effects on fMRI data, patients did not receive their usual medication on the day of scanning. All subjects had provided informed consent in writing.

II. METHODS

Technology has improved fMRI in recent years. Three advances are worth mentioning: Higher field strength, parallel imaging techniques and high resolution imaging in general. Methodological advancements fall into the

categories of pulse sequences, paradigm designs, and processing methods.

A. Pulse Sequences:

For the past nearly 20 years, fMRI has been performed using essentially the same basic pulse sequence: T2* weighted EPI. The reason for this is because BOLD contrast provides the highest functional contrast to noise ratio, is the most time efficient, is temporally stable (relative to multi-shot imaging), and provides for whole brain coverage in about 2 s. Arterial spin labeling (ASL) based perfusion imaging, while achieving perhaps greater capillary specificity and long term temporal stability (i.e. minimal signal drift relative to BOLD contrast), remains less useful for typical activation studies due to its lower functional contrast to noise, additional time required (for the tagging pulse), and typically incomplete brain coverage with a single RF-pulse "tag." Nevertheless, for studies involving extremely long duration activation and/or rest periods, ASL based perfusion contrast to noise ratio has been shown to be superior to that of BOLD. ASL based perfusion maps are better for multi-subject studies. [13].

B. Paradigm Design:

Paradigm is defined here as the construction, temporal organization structure, and behavioral predictions of cognitive tasks executed by the subject during an fMRI experiment. As a general principle the experimenter has to decide in as much detail as possible what he/she wants from the experiment [14]. The experimental design of an fMRI study is complicated, as it not only involves the standard issues relevant to psychological experiments, but also issues related to data acquisition and stimulus presentation. Not all designs with the same number of trials of a given set of conditions are equal, and the spacing and ordering of events is critical. What constitutes an optimal experimental design depends on the psychological nature of the task, the ability of the fMRI signal to track changes introduced by the task over time and the specific comparisons that one is interested in making. In addition, as the efficiency of the subsequent statistical analysis is directly related to the experimental design, it is important that it be carefully considered during the design process [15].

Currently there are two major classes of fMRI experimental designs: block designs and event-related designs. In the following sections we describe each type and discuss the applications for which they are best suited.

Today, most fMRI research on cognitive processes uses event-related experimental designs, but their application in clinical fMRI faces several technical challenges. Currently, most clinical fMRI procedures use blocked designs. In addition to their simplicity, blocked designs are well suited to clinical fMRI because the primary goal in most clinical applications is to localize an activated brain region rather than define the pattern of connectivity throughout the brain. In fact, all major scanner manufacturers currently offer a so-called real-time fMRI capability, provided that the procedure uses a blocked design. This is often an optional software and hardware package that promotes the routine use of clinical fMRI. Nevertheless, because event-related designs offer greater flexibility, they are likely to gain wider acceptance in the future [2].

a. Block Designs: It is an experimental design in which several stimuli are presented one after the other in blocks. In a block design the different experimental conditions are separated into extended time intervals, or blocks. For example, one might repeat the process of interest (e.g., finger tapping) during an experimental block (A) and have the subject rest during a control block (B); The A–B comparison can then be used to compare differences in signal between the conditions. In general, increasing the length of each block will lead to a larger evoked response during the task. This increases the separation in signal between blocks, which, in turn, leads to higher detection power [15].

The main advantages to using a block design are that they offer high statistical power to detect activation and are robust to uncertainties in the shape of the hemodynamic response function (HRF). The latter advantage is due to the fact that the predicted response depends on the total activation caused by a series of stimuli, which makes it less sensitive to variations in the shape of responses to individual stimulus. The flip side is that block designs provide imprecise information about the particular processes that activated a brain region and cannot be used to directly estimate important features of the HRF (e.g., onset or width) [15]. Blocked designs use a boxcar waveform that has a control condition, e.g. resting, and a task condition, typically alternating every 10–30 s [2].

b. Event-Related Designs: It is an experimental design in which trains of single stimuli are presented. In an event-related design the stimulus consists of short discrete events (e.g., brief light flashes) whose timing can be randomized; with two conditions (A) and (B) as given above in Block Design. These types of designs are attractive because of their flexibility and that they allow for the estimation of key features of the HRF (e.g., onset and width) that can be used to make inference about the relative timing of activation across conditions and about sustained activity. Event-related designs allow one to discriminate the effects of different conditions as long as one either intermixes events of different types or varies the inter-stimulus interval between trials. Another advantage to event-related designs is that the effects of fatigue, boredom and systematic patterns of thought unrelated to the task during long inter-trial intervals can be avoided. A drawback is that the power to detect activation is typically lower than for block designs, though the capability to obtain images of more trials per unit time can counter this loss of power [15].

Event-related fMRI is the fMRI technique that can pinpoint the haemodynamic response to single stimuli. It models fMRI signal changes associated with single behavioral trials as opposed to blocks of behavioral trials [12].Event-related designs use very brief stimuli, typically < 1 s in duration, against a background control condition [2].

C. Processing Methods:

One of the most exciting directions to recently emerge in fMRI processing is the use of multivariate analysis, machine learning and pattern classification techniques [13].FMRI Methodology/Paradigms include the following [12]:

a. Activation Paradigm: A paradigm used in functional imaging studies, in which the neural response to a task of interest is compared to the brain's functional activity during a period of rest or during a neutral condition matched for perceptuo-motor components. FMRI

typically assesses differences between neural states, and is therefore ideal for studies of brain activation. Early functional imaging studies with PET often assessed resting brain activity. More recent studies employ Activation Paradigms to assess the brain's response to a specified cognitive task. Careful experimental design ensures that the subsequent difference between the active and control condition 'reflects' the brain's response to the cognitive process of interest. The temporal resolution of the fMRI technique is such that both Blocked (several stimuli presented sequentially in blocks) and Event-Related (trains of single stimuli) experimental designs are possible.

b. ***Counting Task:*** A control task used in functional imaging studies of word generation. Subjects are required to count from one until cued to stop.

c. ***Continuous Performance Test (CPT):*** A random sequence of stimuli is presented over an extended period of time. Subjects are required to respond to a target by pressing a button. They are thus required to maintain their attention and performance over time.

d. ***Haemodynamic Response:*** The movements of the blood and the forces involved in regional blood circulation related to neural activity.

e. ***Nitrous Oxide Technique:*** An early functional imaging technique that measured the differences between the arterial input and venous outflow of nitrous oxide, from which cellular uptake could be determined. It is capable of determining global but not regional changes in blood flow.

f. ***Paramagnetic:*** Para magnetism is the ability of an otherwise nonmagnetic material to exhibit magnetic properties in the presence of a magnetic field. Deoxyhemoglobin is paramagnetic which slightly increases local magnetic field. Magnetic field around deoxyhemoglobin causes nearby protons to lose their radiofrequency energy more rapidly thus lower the MR signal, image appears darker.

g. ***Positron Emission Tomography (PET):*** PET measures the breakdown of radioactive materials within the body. By using radioactive tracers that are attached to biologically important molecules (such as water or glucose), it can measure aspects of brain function such as blood flow or glucose metabolism. PET showed that it was possible to localize mental functions in the brain, providing the first glimpses into the neural organization of cognition in normal individuals (e.g., MI Posner, SE Petersen, PT Fox, ME Raichle, 1988). However, the use of PET was limited due to safety concerns about radiation exposure, image resolution was fairly poor (10-20mm), No temporal information, each scan was of fairly long which was not suitable for some experimental conditions and due to the scarce availability of PET systems.

h. ***Single Positron Emission Computed Tomography (SPECT):*** Like PET, SPECT is a functional imaging technique that produces an image of the distribution in the brain of radio nuclides. In contrast to PET, however, radio nuclides are used that emit a single photon, of lower energy than the two emitted by PET radio nuclides. Thus SPECT has lower detection sensitivity than PET.

i. ***Structural Equation Modeling:*** Models data according to the variance-covariance structure rather than considering variables individually.

j. ***Tower of Hanoi Test:*** The goal of this test is to rearrange a tower of discs of decreasing size on a defined stick with the fewest moves. Subjects can only move one disc at a time, and cannot stack a bigger disc on top of a smaller one. This test assesses problem solving and planning.

k. ***Two-Back Task:*** A version of the N-back working memory task. In this task, the numbers 1 to 4 are displayed randomly. In the no-back sensory motor control condition, subjects press the button corresponding to the number seen on the screen, whereas in the two-back condition, they are required to press the button corresponding to the number seen two stimuli previously.

l. ***Verbal Fluency Task:*** Activation task used in functional imaging studies of word generation. Subjects are required to generate as many words as possible beginning with a specified letter of the alphabet.

m. ***Wisconsin Card Sorting Test (WCST):*** In the classic version of this test subjects are required to match a response card with one of four reference cards according to color, number or shape, and to find the rule that governs correct matching. After an unpredictable number of trials the rule is changed. The test measures flexibility in thinking, the capacity to form abstract concepts, and the ability to shift or maintain attentional set.

n. ***Facial Emotions for Brain Activation (FEBA) Test:*** It is used to examine emotion discrimination ability where, the stimuli consists of colored photographs of faces balance with regard to age, sex, and ethnicity showing different emotional facial expressions (happy, sad, angry, fearful) or no emotion (neutral) [16].

o. ***Model-Driven Approach using Regions of Interest (ROI):*** Model-driven approaches based on prior knowledge about the regions of interest (ROI) that are believed to be relevant to schizophrenia, or model-based functional clustering [17].

p. ***Data-Driven Approach:*** Data-driven approaches based on various features extracted from the fMRI data, such as standard activation maps and a set of topological features derived from functional networks [17].

III. FMRI DATA ACQUISITION

The process of data acquisition is very flexible in fMRI and is paramount to an effective study design. Parameters in influencing temporal and spatial resolution, as well as image acquisition plane and considerations regarding scanner acoustic noise can be used in different settings, providing a wealth of options. BOLD is the most used technique, mainly because of its practical and easy implementation. On the other hand it has limitations, since the nature of the signal measured is not quantifiable or related to a specific physiological parameter, rather it is a complex interplay between cerebral blood flow, volume, and cerebral metabolic rate of oxygen (CMRO2).

Ideally, one should acquire more than just the image information during an fMRI experiment. Behavioral data are crucial to correct interpretation of the data and are sometimes used to model the expected HRF. The magnetic environment

of the scanner room is a challenge to the use of electronic equipment conventionally used to collect subject responses, or measure physiological parameters [14].

The data collected during an fMRI experiment consists of a sequence of individual magnetic resonance images, acquired in a manner that allows one to study oxygenation patterns in the brain. Therefore, to understand the nature of fMRI data and how these images are used to infer neuronal activity, one must first study the acquisition of individual MR images [15].

To construct an image, the subject is placed into the field of a large electromagnet. The magnet has a very strong magnetic field, typically between 1.5–7.0 Tesla which aligns the magnetization of hydrogen, (where 1 Tesla=10,000 Gauss, Earth's magnetic field = 0.5 Gauss, 3 Tesla is 60,000 times stronger than the Earth's magnetic field) atoms in the brain. Within a slice of the brain, a radio frequency pulse is used to tip over the aligned nuclei. Upon removal of this pulse, the nuclei strive to return to their original aligned positions and thereby induce a current in a receiver coil. This current provides the basic MR signal. A system of gradient coils is used to sequentially control the spatial in homogeneity of the magnetic field, so that each measurement of the signal can be approximately expressed as the Fourier transformation of the spin density at a single point in the frequency domain, or k-space as it is commonly called in the field [15].

The image acquisition method used for BOLD fMRI is designed for T2* weighting with a fast imaging readout. In most fMRI experiments the gradient echo method is used. TE is typically in the range of 20–40ms, and TR is selected from 1000ms to 4000ms depending on the required temporal resolution. Although the use of short TR's (e.g. < 1000ms) can improve temporal resolution, it decreases the BOLD signal and limits the number of slices that can be acquired. For this reason it is not generally used in clinical fMRI, which is performed on individual patients and therefore requires the greatest MR signal for both sensitivity and reliability. Single shot EPI is implemented by manufacturers on most state-of-art clinical systems and is widely used for fast image acquisition.

Single shot EPI is preferred to multi-shot EPI, as it minimizes the motion artifacts that are more likely to occur in patients with functional impairment due to their physical condition. Spiral imaging, which is available on some systems, can also be used. Most fMRI exams use an imaging matrix of 64 x 64 and an FOV of 240 mm, giving an in-plane resolution of 3.7 x 3.7 mm [2].

IV. FEATURE EXTRACTION

Feature extraction process can be defined as the procedure of extracting relevant information from an image. This information must be valuable to the later step of identifying the subject with an acceptable error rate. The feature extraction process must be efficient in terms of computing time and memory usage. The output should also be optimized for the classification step. Feature extraction involves several steps - dimensionality reduction, feature extraction and feature selection. The performance of a classifier depends on the amount of sample images, number of features and classifier complexity. A feature extraction algorithm extracts features from the data. It creates those new features based on transformations or the original data. On the other hand, a feature selection algorithm selects the best subset of the input feature set. It discards non-relevant features. Feature selection is often performed after feature extraction.

Some widely used feature extraction algorithms used in literature are:

A. Independent Component Analysis:

Independent Component Analysis aims to transform the data as linear combinations of statistically independent data points. Therefore, its goal is to provide an independent rather that uncorrelated image representation. ICA is an alternative to PCA which provides a more powerful data representation. It's a discriminant analysis criterion, which can be used to enhance PCA.

B. Principal Component Analysis:

It is a mathematical procedure that performs a dimensionality reduction by extracting the principal components of the multi-dimensional data. The first principal component is the linear combination of the original dimensions that has the highest variability. The n-th principal component is the linear combination with the maximum variability, being orthogonal to the n-1 first principal components.

C. Feature Selection:

Feature selection algorithm's aim is to select a subset of the extracted features that cause the smallest classification error. The importance of this error is what makes feature selection dependent to the classification method used. The most straightforward approach to this problem would be to examine every possible subset and choose the one that fulfills the criterion function. However, this can become an unaffordable task in terms of computational time. The idea is to create an algorithm that selects the most satisfying feature subset, minimizing the dimensionality and complexity.

D. Classification:

Image analysis basically involves the study of feature extraction, segmentation, and classification techniques. The input image is first preprocessed, which may involve restoration, enhancement or just proper representation of the data. Then certain features are extracted for segmentation of the image into its components- for example, separation of different objects by extracting their boundaries. The segmented image is fed into a classifier. Image classification maps different regions or segments one of several objects, each identified by a label. Sometimes two or more classifiers are combined to achieve better results. Classification algorithms usually involve some learning - supervised, unsupervised or semi-supervised. Unsupervised learning is the most difficult approach, as there are no tagged examples. Consequently, e.g. most face recognition systems implement supervised learning methods. There are also cases where the labeled data set is small. Sometimes, the acquisition of new tagged samples can be infeasible. Therefore, semi-supervised learning is required.

a. ***Classifiers:*** There are three concepts that are key in building a classifier - similarity, probability and decision boundaries.

a) ***Similarity:*** This approach is intuitive and simple. Patterns that are similar should belong to the same

class. The idea is to establish a metric that defines similarity and a representation of the same-class samples. For example, the metric can be the Euclidean distance. It includes methods such as Template Matching which assign sample to most similar template. Templates must be normalized, Self-Organizing Maps (SOM) which assign pattern to nearest node, then update nodes pulling them closer to input pattern.

The SOM provides a quantization of the image samples into a topological space where inputs that are nearby in the original space are also nearby in the output space, thereby providing dimension reduction and invariance to minor changes in the image sample. The convolutional network extracts successively larger features in a hierarchical set of layers and provides partial invariance to translation, rotation, scale, and deformation.

b) Probability: Some classifiers are build based on a probabilistic approach. Bayes decision rule is often used. Bayesian decision rules can give an optimal classifier, and the Bayes error can be the best criterion to evaluate features. Therefore, a posteriori probability functions can be optimal. It includes methods such as Bayesian which assign pattern to the class with the highest estimated posterior probability.

c) Decision Boundaries: This approach can become equivalent to a Bayesian classifier. It depends on the chosen metric. The main idea behind this approach is to minimize a criterion (a measurement of error) between the candidate pattern and the testing patterns. It includes methods such as Support Vector Machines whose the main characteristics of SVMs are: i) that they minimize a formally proven upper bound on the generalization error; ii) that they work on high-dimensional feature spaces by means of a dual formulation in terms of kernels; iii) that the prediction is based on hyper planes in these feature spaces, which may correspond to quite involved classification criteria on the input data; and iv) that outliers in the training data set can be handled by means of soft margins [18].

V. PREPROCESSING

Prior to statistical analysis, fMRI data typically undergoes a series of preprocessing steps aimed at removing artifacts and validating model assumptions. The main goals are to minimize the influence of data acquisition and physiological artifacts, to validate statistical assumptions and to standardize the locations of brain regions across subjects in order to achieve increased validity and sensitivity in group analysis. When analyzing fMRI data it is typically assumed that all of the voxel since a particular brain volume were acquired simultaneously. Further, it is assumed that each data point in a specific voxel's time series only consists of a signal from that voxel (i.e., that the participant did not move in between measurements). Finally, when performing group analysis and making population inference, all individual brains are assumed to be registered, so that each voxel is located in the same anatomical region or all subjects. Without preprocessing the data prior to analysis, none of these assumptions would hold and the resulting statistical analysis would be invalid. The major steps involved in fMRI preprocessing include the following [15]:

A. Slice Timing Correction:

When analyzing 3D fMRI data it is typically assumed that the whole brain is measured simultaneously. In reality, because the brain volume consists of multiple slices that are sampled sequentially and therefor eat different time points, similar time courses from different slices will be temporally shifted relative to one another. The corresponding measured time courses will appear different. Slice timing correction involves shifting each voxel's time course so that one can assume they were measured simultaneously. This can be done either using interpolation or the Fourier shift theorem to correct for differences in acquisition times.

B. Realignment or Motion Correction:

An important issue involved in any fMRI study is the proper handling of any subject movement that may have taken place during data acquisition. Even small amounts of head motion during the course of an experiment can be a major source of error if not treated correctly. Therefore, it is of great importance to accurately estimate the amount of motion and to use this information to correct the images.

The first step in correcting for motion is to find the best possible alignment between the input image and some target image (e.g., the first image or the mean image). A rigid body transformation involving 6 variable parameters is used. This allows the input image to be translated (shifted in the x, y and z directions) and rotated (altered roll, pitch and yaw) to match the target image. Usually, the matching process is performed by minimizing some cost function (e.g., sums of squared differences) that assesses similarity between the two images. Once the parameters that achieve optimal realignment are determined, the image is re-sampled using interpolation to create new motion corrected voxel values. This procedure is repeated for each individual brain volume.

C. Co-Registration of Structural and Functional Images and Normalization:

Functional MRI data is typically of low spatial resolution and provides relatively little anatomical detail. Therefore, it is common to map the results obtained from functional data onto a high resolution structural MR image for presentation purposes. The process of aligning structural and functional images, called co-registration, is typically performed using either a rigid body (6 parameters) or an affine (12 parameters) transformation.

For group analysis, it is important that each voxel lie within the same brain structure for each individual subject. Of course individual brains have different shapes and features, but there are regularities shared by every non-pathological brain. Normalization attempts to register each subject's anatomy to a standardized stereotaxic space defined by a template brain [e.g., the Talairach or Montreal Neurological Institute (MNI) brain].

The main benefits of normalizing data are that spatial locations can be reported and interpreted in a consistent manner, results can be generalized to a larger population and results can be compared across studies and subjects. The drawbacks are that it reduces spatial resolution and may introduce errors due to interpolation.

D. Spatial Smoothing:

It is common practice to spatially smooth fMRI data prior to analysis. Smoothing typically involves convolving the functional images with a Gaussian kernel, often described by

the full width of the kernel at half its maximum height (FWHM). Common values for the kernel widths vary between 4–12 mm FWHM. There are several reasons why it is common to smooth fMRI data. First, it may improve inter-subject registration and overcome limitations in the spatial normalization by blurring any residual anatomical differences. Second, it ensures that the assumptions of random field theory (RFT), commonly used to correct for multiple comparisons, are valid. A rough estimate of the amount of smoothing required to meet the assumptions of RFT is a FWHM of 3 times the voxel size (e.g., 9 mm for 3 mm voxels). Third, if the spatial extent of a region of interest is larger than the spatial resolution, smoothing may reduce random noise in individual voxels and increase the signal-to-noise ratio within the region.

The process of spatially smoothing an image is equivalent to applying a low-pass filter to the sampled k-space data prior to reconstruction. While all the preprocessing steps outlined above are essential for the standard model assumptions required for statistical analysis to hold, generally, it is necessary to study the interactions among the individual preprocessing steps.

VI. FMRI DATA ANALYSIS

There are several common objectives in the analysis of fMRI data. These include localizing regions of the brain activated by a certain task, determining distributed networks that correspond to brain function and making predictions about psychological or disease states. All of these objectives are related to understanding how the application of certain stimuli leads to changes in neuronal activity.

Multiple dependent measures can be used to detect differences in performance and activation patterns. It is important to begin the analysis by looking at the behavioral data generated by the individual subjects. A thorough analysis of reaction time (RT) and accuracy performance will give an indication of how well individual subjects followed instructions and whether they remained on task throughout the scan. Dramatically different performance (among individuals or groups) will likely bias the imaging results. Some degree of variability is inevitable, but subjects who are not performing the task at roughly the same level as the others most likely will have different activation patterns as well. Therefore, important decisions need to be made about inclusion or exclusion of individuals [19].

A. Image Analysis: Pre-processing:

In the imaging analyses one can measure differences in activation for experimental conditions and subject groups in a number of ways. For example, one can compare two conditions to determine the location of activations (regions of interest, ROIs) that differ between conditions or groups. In addition to the location, it is possible to detect differences in the volume of activation (the number of voxels activated) and/or the intensity of activation (the change in signal strength for these voxels). Within group analyses often use t-test or f-map statistics to compare two conditions on one or more of these measures.

Multifactorial analysis of variance (ANOVAs) or general linear models (GLMs) can be used and have several advantages over simple t-test comparisons. In particular, multivariate analyses allow each task condition to be compared simultaneously against all other conditions [19].

Multivariate pattern analysis algorithm was tested in [20] which hypothesis that distributed perceptual representations are impaired in schizophrenia. The accuracy of a multivariate pattern classifier was high for healthy subjects and in close agreement with other studies. Classification accuracy was significantly lower in subjects with schizophrenia.

Examination of regional cerebral blood flow (rCBF) with positron emission tomography during an action attribution task in a group of patients with FRS was presented in [21]. Here data were analyzed with SPM99 (Department of Cognitive Neurology, London, UK). Each subject's Positron Emission Tomography (PET) data were realigned to the first scan of the time series. The estimates extracted from the rigid body transformation (described as three translations (x, y, z) and three rotations about the axes) were used to realign the images and to perform a mathematical adjustment (minimizing the sum of the squares of differences in intensity between each image and the reference) to remove movement-related components [21].

Paper [22] aimed to explore whether hippocampus dysfunction contributes to schizophrenia-related encoding deficits and it addresses the role of prefrontal cortex dysfunction where SPM2 (Dept. of Imaging Neuroscience, Institute of Neurology, London, UK) was used for pre-processing and data analysis. EPIs were corrected for acquisition delay, realigned, normalized to the MNI stereotactic reference frame (Montreal Neurological Institute; voxel size: 3×3×3 mm), smoothed (Gaussian kernel, 8 mm), and high pass- filtered (128 s). Statistical analysis was carried out using a two-stage mixed effects model. In the first stage, neural activity was modeled by a δ function at stimulus onset for each individual subject. The ensuing blood oxygen-level-dependent (BOLD) response was modeled by convolving these δ functions with a canonical hemodynamic response function (HRF). The resulting time courses were down-sampled for each scan to form covariates in a General Linear Model (GLM). The covariates of the GLM for individual subjects' contrasts were the conditions of interest. Analysis was conducted in [23] using analysis of functional neuro-images (AFNI) (Cox 1996).

B. The General Linear Model Approach (GLM):

The general linear model (GLM) approach has arguably become the dominant way to analyze fMRI data. It models the time series as a linear combination of several different signal components and tests whether activity in a brain region is systematically related to any of these known input functions. The simplest version of the GLM assumes that both the stimulus function and the HRF are known. The stimulus is assumed to be equivalent to the experimental paradigm, while the HRF is modeled using a canonical HRF, typically either a gamma function or the difference between two gamma functions. While the GLM is a simple and powerful approach toward modeling the data, it is also extremely rigid. Even minor mis-modeling (e.g., incorrect stimulus function or HRF) can result in severe power loss, and can inflate the false positive rate beyond the nominal value. [15].

VII. CONCLUSION

There has been an explosive interest in the use of fMRI in recent years. The rapid pace of development and the interdisciplinary nature of the neurosciences present an

enormous challenge to researchers. Although fMRI provides a safe and reliable method for exploring the brain structures and networks that underlie cognitive abilities, a great deal of care is needed when acquiring and analyzing developmental data.

This paper attempts to focus on schizophrenia, symptoms of schizophrenia along with its categories, its causes and treatment, methods used for FMRI, data acquisition, feature extraction, preprocessing of FMRI data and its analysis.

Observing differences between a group of control subjects and a group of schizophrenic patients always raise the question of whether these differences are a genuine consequence of the disease or an effect of the administered drugs. The modifications of the connectivity within the frontal lobe appear as a good support of some cognitive dysfunctions observed in schizophrenia.

Literature review confirms that, the most popular multivariate methods to analyze fMRI data is independent component analysis (ICA). ICA is proved to be more consistent and robust, hence improving the ability to develop reliable biomarkers for disease classification. PCA is the most widely used method to study functional connectivity, and allows decomposing neuroimaging data into a set of modes. Data were analyzed using Statistical Parametric Mapping (SPM).

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IX. REFERENCES

[1]. Nikos K. Logothetis, "What we can do and what we cannot do with fMRI" Vol 453, Nature Neuroscience Journal, 12 June 2008.

[2]. H. Mao and G. S. Berns, "MRI in the study of brain functions: clinical perspectives" April 2002.

[3]. Peter Bandettini, "Functional MRI today", International Journal of Psychophysiology 2007 p.138–145.

[4]. Mary-Ellen Lynall, Danielle S. Bassett "Functional Connectivity and Brain Networks in Schizophrenia" The Journal of Neuroscience, July, 2010.

[5]. Sjoerd J. H. Ebisch, Anatolia Salone, "Out of touch with reality? Social perception in first-episode schizophrenia", Oxford University Press, January 2012.

[6]. Kuperberg GR, West WC, Lakshmanan BM, Goff D. "Functional Magnetic Resonance Imaging Reveals Neuroanatomical Dissociations During Semantic Integration in Schizophrenia", BIOL PSYCHIATRY 2008.

[7]. Whalley HC, Simonotto E, Marshall I, Owens DG, Goddard NH, Johnstone EC, Lawrie SM. "Functional disconnectivity in subjects at high genetic risk of schizophrenia", Oxford University Press, Brain 2005.

[8]. Glahn DC, Ragland JD, Abramoff A, Barrett J, Laird AR, Bearden CE, Velligan DI. "Beyond Hypofrontality: A Quantitative Meta-Analysis of Functional Neuroimaging Studies of Working Memory in Schizophrenia", Wiley InterScience, February 2005.

[9]. C. Farrer, N. Franck, C.D. Frith, J. Decety, N. Georgieff, T. d'Amato, M. Jeannerod, "Psychiatry Research: Neuroimaging", 2004, p. 31–44.

[10]. "What is schizophrenia?" By Australian Government under National Mental Health Strategy, May 2007.

[11]. "Schizophrenia", Published by National Institute of Mental Health, USA, September 2009.

[12]. Rachel L.C. Mitchell, Rebecca Elliott and Peter W.R.Woodruff, "fMRI and cognitive dysfunction in Schizophrenia", TRENDS in Cognitive Sciences Vol.5 No.2, Elsevier, February 2001.

[13]. Peter Bandettini, "Functional MRI today" International Journal of Psychophysiology, p. 138–145, 2007.

[14]. Edson Amaro Jr., Gareth J. Barker, "Study design in fMRI: Basic principles", Brain and Cognition, November 2005.

[15]. Martin A. Lindquist, "The Statistical Analysis of fMRI Data", Statistical Sci.,Vol. 23 Num.4, p. 439–464, 2008.

[16]. Seiferth NY, Pauly K, Kellermann T, Shah NJ, Ott G, Herpertz-Dahlmann B, Kircher T, Schneider F, Habel U., "Neuronal Correlates of Facial Emotion Discrimination in Early Onset Schizophrenia", Neuro psychopharmacology 34, 477–487, 2009.

[17]. Guillermo A. Cecchi, Irina Rish et al, "Discriminative Network Models of Schizophrenia", November 2009.

[18]. Pritesh G. Shah, "Multi-View Face Recognition: A Review" International Conference on Advances in Computing and Management, ISBN 978-81-921768-0-2, January 06-08, 2012.

[19]. M.C. Davidson, K.M. Thomas, and B.J. Casey, "Imaging the Developing Brain With fMRI", Mental Retardation and Developmental Disabilities Research Reviews 9: 161–167, 2003.

[20]. J.H. Yoon, "Multivariate Pattern Analysis of Functional Magnetic Resonance Imaging Data Reveals Deficits in Distributed Representations in Schizophrenia", BIOL PSYCHIATRY 2008.

[21]. C. Farrer, N. Franck, C.D. Frith, J. Decety, N. Georgieff, T. d'Amato, M. Jeannerod,. "Neural correlates of action attribution in schizophrenia" Psychiatry Research: Neuroimaging 131, p. 31–44, 2004.

[22]. Zierhut, K., "The role of hippocampus dysfunction in deficient memory encoding and positive symptoms in schizophrenia", Psychiatry Research: Neuroimaging (2010).

[23]. McDowell JE, Brown GG, Paulus M, Martinez A, Stewart SE, Dubowitz DJ, Braff DL. , "Neural Correlates of Refixation Saccades and Antisaccades in Normal and Schizophrenia Subjects", Society of Biological Psychiatrym 2002.