

Brief Report
Neuro-imaging in Mental Health
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Functional neuro-imaging has rapidly developed as a powerful tool in cognitive neuroscience and, in recent years, has seen widespread application of it in psychiatry. Although such studies have produced evidence for abnormal patterns of brain response in association with some pathological conditions, the core pathophysiologies remain unresolved. Although imaging techniques provide an unprecedented opportunity for investigation of physiological function of the living human brain, there are fundamental questions and assumptions which remain to be addressed. We consider the difficulties that accompany the most frequent application of these techniques—an attempt to identify responses of the brain to changing tasks or contexts—and explore how these responses are affected by psychiatric illness. These are critical issues. If these cannot be addressed, functional imaging approaches must confine their ultimate aims to diagnosis and accept that they will never clarify etiology. If the following questions remain unanswered, no matter how complex their technical advances are, the techniques will inevitably produce ambiguous findings. The questions are (1) Has the psychiatric disorder under study been appropriately specified? (2) Has the chosen task enabled a clear and unambiguous manipulation of the psychological processes that we wish to study? (3) How may we interpret changes in brain activations in the patient group?

Key words: Functional Neuro-imaging, Psychiatry, EEG, MRI, PET

Since the development of first functional brain imaging technique used in human beings by Seymour Kety in 1948; functional neuro-imaging has advanced in such a way that today it provides the crucial link between clinical features of several psychiatric disorders and their corresponding dysfunctional brain systems. By showing the various stages in the cascade from neuronal activity to behaviour, functional neuro-imaging scores over the conventional structural neuro-imaging as the latter points out only the details of structures of brain without offering any implication they have on behaviour. Functional neuro-imaging quite rightly, therefore, is considered the spearhead of a neuropsychiatric perspective.

Today functional neuro-imaging is used in research purposes. Though limited by cost, it can also be used as an important diagnostic aid. Moreover investigation like trans-cranial magnetic stimulation offers the advantage of its use as an efficacious intervention technique as well.

With the advances in technology various devices for detecting more specific functional aspects came up. Now to select a suitable mode of investigation we have plenty of options to choose from e.g. PET, SPECT, xenon enhanced CT, fMRI to detect blood flow and perfusion; MRS, PET to gain information about metabolism; SPECT & PET for ligands and neuro-receptor imaging and lastly EEG, MEG and TMS for electrophysiology.

Surprisingly, unlike the measurement of brain structure measurement of brain function has not been used much extensively in clinical practice. Its main application has been in research, though clinicians opine that alterations in brain function must at some level underlie all disorders in psychiatry. So, in the near future, it can be expected that functional neuro-imaging will gain popularity among the clinicians and will gain the status of an essential rather than optional mode of investigation.

Functional neuro-imaging techniques

Positron emission tomography (PET). PET is named from its use of positron emitting isotopes to image brain functioning. Positron emitting isotopes are very short lived radioactive entities including oxygen 15 (^{15}O), nitrogen 13 (^{13}N), carbon 11 (^{11}C), and fluorine 18 (^{18}F). The radioactive isotopes are incorporated into specific molecules to study cerebral metabolism, blood flow, and neuro-receptors. Most commonly used are, ^{15}O , water for cerebral blood flow studies or ^{18}F , flouorodeoxyglucose (FDG) to image metabolism (Berman & Weinberger, 1991; Nadeau & Crosson, 1995).

Radioactive agents are intravenously injected into the subject, whose head is positioned within a radiation detector. The radioactive isotope decays within the brain, releasing a positron. The positron travels a short distance and collides with an electron, resulting in the emission of two photons that travel at 180° to each other at the speed of light. The photons are detected at the opposite sides of the head simultaneously, and the location of the emitting positron can thus be calculated (Berman & Weinberger, 1991).

Advantages. PET is used extensively to understand normal brain functioning, to image neurotransmitter and their receptors and cerebral blood flow. It has greater spatial resolution than SPECT. Only PET can measure cerebral glucose metabolism. Because of shorter half life of tracer, PET studies can often be conducted multiple times in a day.

Single photon Emission computed tomography (SPECT).

SPECT also uses radioactive compounds to image brain activity. Like PET, SPECT derives its name from the type of radioisotope involved, compounds that produce only one photon per disintegration. The radioisotopes are readily available from commercial sources. This makes SPECT available in most clinical centers. However, because SPECT imaging depends on a single photon being released, its spatial resolution is less than that of PET.

Advantages. It produces both quantitative and qualitative measures of cerebral blood flow. It may be beneficial in diagnosing dementing illness, and is more affordable than PET.

Functional magnetic resonance imaging (fMRI).

Functional MRI couples the exquisite spatial resolution of structural MRI with the ability to image areas related to neural activity. It does this noninvasively, without the use of radioactive agents. When a localized region of brain tissue becomes active, it uses oxygen and glucose and produces certain metabolic byproducts. In these areas of increased neural activity, the metabolism and blood flow increase with the increased energy demands.

The cerebrovascular physiology of the brain is such that local blood flow and volume increases to supply the needed fuel and remove the metabolic waste products. Although the exact mechanism remains to be determined, many scientists believe that the supply of oxygen is much greater than what neurons utilize. This results in an actual increase in the concentration of oxygenated hemoglobin compared with deoxygenated hemoglobin in areas of neural activity. Oxygenated hemoglobin is less paramagnetic and has increased intensity (looks brighter) compared with deoxygenated hemoglobin on images created with T_2 weighted pulse sequences. fMRI uses this blood oxygen level dependent (BOLD) effect to image changes in neural activity (Kwong, et al., 1992). In fMRI measures of activation are always relative as they do not directly assess absolute changes in blood flow. So cognitive tests are given which serves as probes to activate specific neural network.

Advantages. Because fMRI requires no radiation and can be completely non invasive, a participant can be imaged multiple times. It also removes ethical constraints about imaging children and adolescent with psychiatric illnesses. fMRI is performed in standard, clinically available 1.5 Tesla, magnetic resonance scanner so it is a readily available mode of investigation.

Magnetic resonance spectroscopy (MRS). MRS is performed in the same scanners as structural and functional MRI. However, by altering the scanning parameters, the signal represents chemical entities from brain areas. The response of an atom in a magnetic field is characteristic, based on the number and nature of its subatomic particles, as well as its unique molecular environment. Spectra are obtained that are characteristic for nuclei within certain molecules (McClure, Kanfer, Panchalingam, Klunk, & Pettegrew, 1995). This principle is employed in MRS to study the concentration of brain metabolites. Typically, spectra are obtained from a number of nuclei, including ^1H , ^{13}C , ^{23}Na , ^7Li , and ^{31}P .

In psychiatry, investigators are primarily using ^1H and ^{31}P MRS. Proton (^1H) spectroscopy can distinguish N acetyl aspartate (NAA), creatine and phosphocreatine, and phosphatidylcholine. Signals can be obtained from glutamate, GABA, lactate, and inositol phosphates, although these signals may be difficult to adequately resolve (Narayana & Jackson, 1991). NAA is found in neurons and is absent in most glial cell lines. Decreases in NAA may reflect a diminished number or density of neurons; NAA levels decrease proportionate to the brain loss in neurodegenerative disorders (Maier, 1995). Creatine and phosphocreatine are important energy substrates, and phosphatidylcholine is an important component of cell membranes (Narayana & Jackson, 1991).

MRS with ^{31}P detects the relative tissue concentrations of certain phosphorous metabolites, including those involved in energy and phospholipid metabolism (Waddington, O'Callaghan, Larkin, 1990). Resonances are obtained from the precursors and breakdown products of membrane phospholipids (phosphomonoesters and phosphodiesteres respectively), which uncover potential abnormalities in membrane turnover. To reflect energy metabolism, ^{31}P MRS senses phosphocreatine, adenosine triphosphate, adenosine diphosphate, and inorganic orthophosphate; intracellular pH can also be assessed (Pettegrew, 1991).

Advantage. MRS is able to measure concentration of some drugs in the brain including lithium and fluoxetine.

Magnetoencephalography (MEG). Reading of brain electromagnetic activity is the basis of MEG. All electrical sources generate magnetic field. Electrical sources within the brain have been modeled as electrical dipoles consisting of assemblies of neurons oriented in tangential (i.e. parallel to the skull) or radial (i.e. perpendicular to the skull) direction. MEG utilizes a device called superconducting quantum interference device (SQUID) magnetometer to detect these magnetic fields within the brain. This is a supercooled detection coil that is extremely sensitive to low intensity magnetic fields generated by dipoles within the brain.

Advantage of MEG over EEG. SQUID need not be in contact with the scalp and it is insensitive to the effects of muscle tension and activity.

- Relatively unaffected by the interposed structure like skull, scalp.
- Detects sources deep within the brain.
- Relatively unaffected by surrounding fields.
- Better temporal resolution

Electroencephalography (EEG). A method of recording graphically the electric activity of the brain, particularly the cerebral cortex, by the means of electrodes attached to the scalp. The conventional EEG parameters are obtained from averaged EEG power spectra, based on periods of time and broad fixed frequency band for a specific lead. This approach of averaging of EEG signal masks the dynamic and temporal structure of EEG, leading to complicated data interpretation.

Technical advancement of EEG equipment in the last three decades has also facilitated quantitative analysis of EEG data. Quantitative EEG, also known as neurometrics or brain mapping, is a method of paperless recording using computer-based instrumentation. There are various advantages compared to conventional EEG, including storage, acquisition, quantification, automatic spike detection, and automatic event detection. Quantitative EEG has provision for making changes in the recorded parameters, such as montage, filter.

Spectral analysis. In this technique, a series of segments (epochs) of EEG data (commonly one to four seconds in length) are processed through Fourier transformation to calculate the energy (power) in the signal that can be accounted for by a series of sinusoidal waveform of different amplitudes and frequencies. It represents state of neuronal activity in the brain.

Coherence or synchronization. It measures synchronized brain electrical activity from different region within an individual which reflects both the structural and functional connections between brain

areas. A decrease in coherence between two regions presumably indicates a decrease in their functional connection and vice-versa. Used for assessing anatomical/functional binding and metabolism in brain.

Evoked potentials (EP). In this paradigm, electrical activity is recorded while the subjects are exposed to repetitive visual (i.e. flashes of light or pattern), auditory (i.e. clicks or tones) or other stimuli (i.e. electrical stimulation of the skin). A computer averages the response to time locked, repeated stimuli, thus enhancing the signal evoked by the stimuli while averaging out other brain activity unrelated to the stimuli. The resulting display is a voltage waveform of the average response potentials. These potentials appear as a series of positive and negative waveforms occurring at specific time intervals following a stimulus and are labeled according to their polarities (P for positive, N for negative) and latencies from time of the stimulus (in milliseconds). It is used to assess rapidity and level of processing of brain.

Transcranial magnetic stimulation (TMS). TMS refers to an in vivo technique of delivering magnetic pulses to the cortex with a handheld stimulating coil, which is applied directly to the head. The equipment necessary for delivering TMS consists of two parts: a stimulator, which generates brief pulses of strong electrical currents whose frequency and intensity can be varied, and a stimulation coil connected to the stimulator. TMS stimulates the cortex focally and painlessly by creating a time-varying magnetic field. This localized pulsed magnetic field over the surface of the head induces electrical currents in the brain, which then depolarizes underlying superficial neurons.

TMS methods have been applied in a number of ways to probe the function of various aspects of the normal and abnormal brain in human subjects.

Cortical Stimulation.

Cortical and regional connectivity

Cortical plasticity

Cognition

Neuro-imaging Findings in Major Psychiatric Illnesses

Schizophrenia.

PET and SPECT studies. During the resting state. The first functional cerebral abnormality reported in older schizophrenic patients was a reduction in frontal blood flow, or hypofrontality (Ingvar &

Franzen, 1974). This finding spawned a number of studies, patient populations have ranged from acutely ill, never medicated adolescents to patients receiving long term medication. Hypofrontality is an inconsistent finding and probably depends on many factors (Berman & Weinberger, 1991, 1999; Chabrol, Guell, Bes, & Moron, 1986; Cleghorn et al., 1989; Early, Reiman, Raichle, & Spitznagel, 1987; Gur et al., 1995; Paulman, et al., 1990; Tamminga et al., 1992). In fact, some investigators find hyperfrontality in unmedicated schizophrenic patients (Ebmeier et al., 1993). Several PET studies implicate basal ganglia dysfunction in schizophrenia (Wong, et al., 1986; Liddle et al., 1992; Cleghorn et al., 1992).

During cognitive tasks. By imaging participants during the performance of tasks, cerebral activity patterns reflect a state with less variability due to random, task independent thought processes. Schizophrenic individual invariably show dysfunction within fronto-parietal- temporal networks regardless of the task used (O'Driscoll et al., 1999; Guenther et al., 1991; Cohen, Semple, Gross, & Nordahl, 1988; 1995; Carter, Mintun, Nichols, & Cohen, 1997; Gur, Jaggi, Shtasel, Ragland, & Gur, 1994; Weinberger, Berman, & Illowsky 1988; Rubin, 1991; Berman, Torrey, Daniel, & Weinberger, 1992; Andreasen, 1992).

fMRI studies. Overall studies have reported reduced limbic activation in the schizophrenia for given cognitive task (Frith et al., 1995; Honey et al., 2000).

MRS studies. ^{31}P MRS has been used to investigate membrane components and high energy phosphate compounds in the left dorsolateral prefrontal cortex of drug naive patients with first episode of schizophrenia, patients with chronic schizophrenia, and healthy control subjects. All patients with schizophrenia, whether acute, drug naive, or chronic, showed decreased levels of phosphomonoesters, the building blocks for cell membranes (Pettegrew et al., 1991; Stanley et al., 1995). However, other groups have reported increased phosphodiesteres even in chronic patients (Deicken et al., 1994).

In ^1H MRS studies schizophrenic patients showed reduced NAA in mesial temporal lobe and dorsolateral prefrontal cortex (Buckley et al., 1994; Bertolino, Esposito et al., 2000; Delamillieure et al., 2000; Deicken et al., 2000)

EEG studies. Numerous qualitative studies indicate abnormal conventional EEG findings in 20% to 60% of schizophrenic patients (Small, 1993; Small, Milstein, Sharpley, Klapper, & Small, 1984).

Evaluation of EEG and QEEG literature on schizophrenia is complicated by the evident heterogeneity of the illness. Most often, the reported abnormalities have been delta and/or theta excesses in frontal areas (Primavera, Fonti, Novello, Roccatagliata, & Cocito, 1994; Fenton, Fenwick, Dollimore, Dunn, & Hirsch, 1980; Morihisa, Duffy, & Wyatt, 1983; Dierks, Maurer, Ihl, & Schmidtke, 1989; Kemali et al., 1980; Galderisi et al., 1992) a decreased mean frequency and lower power in the alpha band (Small, Milstein, Sharpley, Klapper, & Small, 1984; Shagass, 1977; Fenton et al., 1980; Merrin & Floyd, 1992), and increased beta power (Laurian et al., 1984; Kemali et al., 1986; Karson, Coppola, & Daniel, 1988). Increased anterior coherence also has often been reported (Nagase, Okubo, Matsuura, Kojima, & Michio, 1992).

In this institute Agarwal and Nizamie (2003) found a significantly less interhemispheric gamma coherence across all brain area in schizophrenics and further Bandopadhyaya and Nizamie (2005) found more so in temporal area.

ERP Studies. The P300 ERP, a positive deflection occurring approximately 300 milliseconds after the introduction of a stimulus, is regarded as a putative biological marker of risk for schizophrenia (Bharath, Gangadhar, & Janakiramaiah, 2000; Blackwood, 2000). The P300 amplitudes are smaller in patients with schizophrenia and is one of the most replicated electrophysiological findings (Bruder, 1999; Mccarley et al., 1997). Latency of P300 was prolonged and value was maximum in left central (C3) and frontal region in drug naïve and drug free schizophrenics (Simlai & Nizamie, 1998).

Abnormalities in the N400 amplitude in schizophrenia have been reported (Niznikiewicz et al., 1997; Nestor et al., 1997; Mathalon, Faustman, & Ford, 2000). Investigators suggest that individuals with schizophrenia do not use the context of the preceding portion of the sentence and fill in responses to phrases based on the immediately preceding word rather than the whole sentence or passage

Mood disorder.

PET and SPECT studies. Studies revealed decreased blood flow and metabolism in subgenual prefrontal cortex (SGPFC) (Drevets, Price, & Simpson 1997) in bipolar depressed patients. Whereas manic patients showed increased in SGPFC (Blumberg et al., 2000; Strakowski, 2002) and basal ganglia (O'Connell et al., 1995; Blumberg et al., 2000).

fMRI studies. During motor performance, manic bipolar patients had significantly higher activation in right globus pallidus compared with bipolar depressed patients (Caliguri et al., 2003). During stroop task, manic patients showed decreased right ventral prefrontal cortical activation whereas depressed patient showed an area of increased activation compared with euthymic patients (Blumberg, Leung, Skudlarski, Lacadie, Fredericks, Harris, Charney, Gore, Krystal, & Peterson, 2003). During verbal fluency task, bipolar patients had increased prefrontal cortical activation compared with healthy controls (Curtis et al., 2001). Because of wide variability of cognitive task employed comparison of fMRI studies are inevitably hampered.

MRS studies. MRS studies have reported elevated choline concentrations in the striatum of bipolar patients (Strakowski, 2002). Decreased NAA in the dorsolateral prefrontal cortex was found in bipolar children and adolescents with parental bipolar disorder (Chang et al., 2003), in bipolar adults (Winsberg et al., 2000) and in manic patients. Davanzo et al. (2001) and Cecil et al. (2003) found a nonsignificant elevation in myo-inositol concentration in bipolar children compared with healthy subjects, suggesting that elevated myo-inositol may be a biological marker for early onset of affective disorder.

Using MRS to examine medication effect, Moore, Bebchuk et al. (1999) reported a decrease in anterior cingulate myo-inositol following lithium treatment. Lithium has also been shown to increase NAA in frontal, temporal, parietal and occipital lobes of bipolar patients, which has been interpreted to suggest that lithium may be neuroprotective (Moore et al., 2000; Silverstone et al., 2003).

EEG studies. The incidence of abnormal conventional EEG findings in mood disorders appears to be substantial, ranging from 20% to 40% (Small, 1993; Taylor & Abrams, 1981; Cook, Shukla, & Hoff, 1986; McElroy, Keck, Pope, & Hudson, 1988) higher in 1) manic than depressed patients, 2) female than male bipolar patients, and 3) nonfamilial cases with late-age onset. EEG studies report that small sharp spikes and paroxysmal events are often found, especially on the right hemisphere (Struve, Saraf, Arko, Klein, & Becka, 1977). There is broad consensus in QEEG studies that increases in alpha or theta power, as well as asymmetry and hypocoherence in anterior regions, appear most often in unipolar depressed patients (Monakhov & Perris, 1980; Itil, 1983; Nystrom, Matousek, & Hallstrom, 1986; Knott & Lapierre, 1987; Pollock & Schneider, 1990; Nieber & Schlegel, 1992; Ramanan & Nizamie,

1997). Bipolar patients often display decreased alpha activity (Knott & Lapierre, 1987; Clementz, Sponheim, Iacono, & Beiser, 1994; Das & Nizamie, 2001) but increased beta activity (Prichep & John, 1986; John, Prichep, Fridman, & Easton, 1988; Das & Nizamie, 2001).

Together, these studies support a model of bipolar disorder that involves dysfunction within subcortical (Striatal thalamic) prefrontal networks and the associated limbic modulating regions (amygdala, midline cerebellum).

Functional imaging in personality disorder.

1. *Schizotypal personality disorders*. SPECT study by. Trestman, Buchsbaum, Siegel, et al. (1995) revealed greater increase in blood flow to dorsolateral prefrontal cortex (DLPFC) during cognitive task. PET studies have shown asymmetry in striatal metabolism (Siegal et al., 1994) and lower glucose metabolism in anterior cingulate (Haznedar et al., 1995). This finding suggest abnormal striated function in schizotypal personality disorder which reflect a particular form of dopaminergic dysfunction in schizophrenia spectrum illness.

2. *Borderline personality disorder*. Goyer et al. (1994) examined regional cerebral metabolic rates of glucose (rCMRG) in patients with personality disorder. They found higher glucose metabolism in the prefrontal cortex, lower metabolism in inferior portions of the frontal cortex, the posterior cingulated, and the left parietal area.

3. *Antisocial personality disorder*. A study by Intrator (1993) utilizing SPECT found that ASPD had more ventral occipital and less temporo-parietal cortical activation than normals with the affective task. Thus this study provides support for the hypothesis that ASPD respond abnormally to stimuli with aversive emotional significance.

Anxiety disorder.

1. *Panic disorder*. PET studies revealed abnormal asymmetry in orbito-frontal and hippocampal region (Nordahl et al., 1998; Bisaga et al., 1998). MRS studies showed increased brain lactate level in patients with panic disorder (Dager et al., 1995). Another study focusing on frontal lobe revealed phosphocreatine asymmetry with levels on the left greater than those on the right (Shioiri et al., 1996). qEEG showed paroxysmal activity in temporal lobe (Jabourian, Erlich, Desvignes, El Hadjam, & Bitton, 1992).

2. *Post Traumatic Stress Disorder (PTSD)*. Increased activity in amygdala, orbitofrontal cortex, insular cortex, anterior temporal pole and

anterior cingulate cortex was seen in subjects of PTSD in PET studies. (Rauch, et al., 1996; Shin et al., 1999). Though, Bremner et al. (1999) reported deactivation in medial prefrontal cortex in similar population.

3. Obsessive compulsive disorder (OCD).

PET studies. Major PET studies found elevated metabolism, or rCBF in the orbitofrontal cortex (Baxter et al., 1988; Swedo et al., 1989; Sawle, Hymas, Lees, & Frackowiak, 1991) or thalamus (Perani et al., 1995; Swedo et al., 1989). There was significant decrease in glucose metabolism in these areas after treatment with clomipramine (Benkelfat, et al. 1990), fluoxetine (Baxter et al., 1992) and paroxetine (Saxena et al., 1999).

SPECT studies

Baseline SPECT studies have found that patient with OCD have increased rCBF in frontal cortex (Machlin et al., 1991; Rubin, Villaneuva-Meyer, Ananth, Trajmar, & Mena, 1992) and decreased in basal ganglia specially caudate nucleus (Adams, Warneke, McEwan, & Fraser, 1989; Lucey et al., 1997). Elevated HAMP AO uptake in OCD patients decreased significantly after treatment with fluoxetine (Hoehn-Saric et al. 1991) and Clomipramine (Rubin et al., 1992).

MRS studies. Bartha et al. (1998) found significantly lower relative level of NAA in the left and right striatum of patient with OCD compared with healthy control subjects.

EEG studies. Increased theta activity has been reported in OCD (Perros et al. 1992; Silverman & Loychik 1990). Sarkar & Sinha (2004) carried out 1st QEEG study to validate fronto subcortical dysfunction hypothesis and found increase theta coherence in OCD patients as compared to normal controls.

To summarized, these studies consistently indicate elevated activity in the orbitofrontal cortex in patients with OCD, with less consistent abnormalities in the caudate nucleus which decreases with the treatment.

Substance Use Disorder

1. Alcohol

PET and SPECT studies. Alcoholics showed decreased metabolism in prefrontal, parietal and temporal cortices (Volkow et al., 1992) increased metabolism in frontal regions during detoxification (Volkow et al., 1995), and significantly lower benzodiazepine distribution

in frontal, anterior cingulate and cerebellar cortices (Abi-dargham et al., 1998).

MRS Studies. Measures of visibility of brain alcohol in-vivo vary widely ranging from 21% to 100% (Moxon et al., 1991; Chiu et al., 1994; Meyerhoff, Rooney, Tokumitsu, & Weiner, 1996; Petroff, Novotny, Ogino, Avison, & Prichard, 1990). NAA/Choline ratio thought to represent neuronal reserve were reduced in frontal, thalamus and cerebellar areas (Jagannathan, Desai, & Raghunathan, 1996).

EEG Studies. Among numerous QEEG studies, there is a consensus of increased beta relative power in alcoholism (Coger, & Dymond, 1979; Coger, Dymond, Serafetinides, Lowenstam, & Pearson, 1978; Bauer & Hesselbrock, 1993; Gabrielli et al., 1982; Lakra & Nizamie, 2002). ERP study suggests a frontal lobe function anomaly in alcoholics (Basu & Nizamie, 2002).

2. Cannabis

PET and SPECT Studies. Studies showed increased regional metabolism in the cerebellum during acute administration of THC, though chronic use showed increased metabolism in the orbitofrontal cortex and cingulated gyrus (Volkow et al., 1996; Mathew et al., 1997).

EEG Studies. Increased alpha power, especially in anterior regions, has been reported in withdrawal, as well as after acute exposure to cannabis (Struve, Straumanis, Patrick, & Price, 1989; Struve, Straumanis, & Patrick 1994).

3. Opiates

PET & SPECT studies. Acute intake of morphine reduced global metabolism by 10% and by about 5-15% in telencephalic areas and the cerebellar cortex (London et al., 1990). Another study revealed significant increase in regional cerebral blood flow in cingulated, orbitofrontal and medial prefrontal cortices, and caudate nuclei (Firestone et al

EEG studies. Increased alpha and decreased delta and theta have been reported in cocaine users in withdrawal Alper et al 1990; Alper, Chabot, Prichep, Kim, & John, 1993; Cornwell, Roemer, Jackson, & Dew 1994; Prichep et al., 1996; Roemer, Cornwell, Jackson, & Dewart, 1994).

Child psychiatric disorder

1. Autism

PET and SPECT studies. Studies have shown temporal and frontal lobe hypoperfusion (Mountz, Tolbert, Lii, Katholi, & Hg 1995, 2000) and abnormal temporal cortex activation during auditory test (Muller et al., 1999; Boddaert & Zilbovicius, 2002).

fMRI studies. Increased activity in the bilateral inferior temporal gyrus, right thalamus, left superior temporal gyrus and left peristriate visual cortex has been found in subjects with autism, but not in healthy controls, when they process facial features (identity) and facial expressions (emotion) (Critchley et al., 2000; Schultz et al., 2000; Ogai et al., 2003).

Ring et al. (2002) investigated executive function in autism, found dysfunctional integration of the dorsolateral prefrontal cortex, posterior cingulate cortex and parietal cortex.

Recently, it was found that the language deficits in autism were subtended by anomalies in the dentothalamo-prefrontal pathway and reverse dominance in the right hemisphere (Belmonte & Yureglun-Todd, 2003).

MRS Studies. Studies have found evidence of decreased synthesis and increased degradation of prefrontal cortical membranes (Minschew, Goldstein, Dombrowski, Panchalingam, & Pettegrew, 1993) and reduced concentration of N-acetyl-aspartate (NAA) in the amygdala, hippocampus, cingulate, cerebellum and vermal area (Chugani, Sundram, Behen, Lee, & Moore, 1999; Otsuka, Harada, Mori, Hisaoka, & Nishitani, 1999; Hisaoka, Harada, Nishitani, & Mori, 2001; Friedman et al., 2003) in subjects with autism.

EEG Studies. A variety of EEG abnormalities may be seen in autistic disorder, including diffused and focal spikes, paroxysmal spike and wave patterns, multifocal spike activity, and a mixed discharge. The

prevalence of EEG abnormalities in autistic disorder (in the absence of a clinical seizure disorder) ranges from 10 to 83 percent and depends on the number of recordings and the nature of the sample obtained (Volkmar, 2005).

EP Studies. Auditory brainstem evoked potentials in autistic disorder indicates no evidence of abnormalities in the auditory brainstem pathways. However, abnormalities of cognitive potentials, particularly the auditory P300 (which represents the brain's processing of sensory stimuli) have been demonstrated in autistic disorder. This presumably reflects abnormalities in higher auditory processing and neural pathways (Volkmar, 2005).

On the basis of these findings, it has been suggested that structural and biochemical abnormalities in neural network involving the fronto-temporo-parietal cortex, limbic system, and cerebellum underlie the pathophysiology of autism.

2. ADHD

PET and SPECT studies. One of the fundamental underlying dysfunction in ADHD is thought to be within the dopamine system. Dougherty et al. (1999) in a SPECT study found a 70% increase in dopamine transporter density in the striatum of adults with ADHD. Another PET study by Ernst et al. (1999) showed a 48% increase of dopamine accumulation in the right midbrain of children with ADHD. These studies indicate that over production of dopamine in the midbrain could be related to increased reuptake of dopamine in the striatum.

fMRI studies. Bush et al. (1999) on testing attention in a group of adult ADHD patients found that they failed to activate the cognitive/attention division of the anterior cingulate gyrus. Similarly, Rubia et al. (1999) and Vaidya et al. (1998) have shown a failure of right prefrontal cortex activation during response inhibition paradigm in boys with ADHD vs. normal controls.

EEG studies. A large percentage of children with attention deficit problems (more than 90%) show QEEG signs of cortical dysfunction, the majority displaying frontal theta or alpha excess, hypercoherence, and a high incidence of abnormal interhemispheric asymmetry (Marosi et al., 1992; Mann et al., 1992).

Dementia

Alzheimer's Disease.

SPECT studies. Studies have shown a temporoparietal hypoperfusion that is typically asymmetric (Goldenberg et al., 1989; Curran et al., 1993). Not all patients with AD show temporoparietal hypoperfusion but AD can be accompanied by a great variety of perfusion patterns, depending on cognitive findings or the severity of illness (McMurdo et al., 1994)

PET studies. Like typical hypoperfusion perfusion patterns visualized by SPECT, PET studies demonstrate a reduced cortical oxygen consumption or glucose metabolism, which is most pronounced and often asymmetrical in temporoparietal areas (Salmon, Sadzot, & Maquet, 1994).

The observed metabolic changes are correlated with test performance, the severity of illness and duration of illness (Kwa, Weinstein, Posthuyms, & Meyjes, 1993).

EEG studies. Studies show decrease of mean frequency (Brenner et al., 1986) of the dominant occipital activity of the alpha: theta ratio and an increase of relative (Coben, Danziger, & Berg, 1983) or absolute theta power, whereas delta power increases in later stages of illness (Prichep et al., 1994).

Where do we stand now?

With the advent, functional neuro-imaging raised hopes of providing the master key to unlock the even unsolved mystery of etiology of psychiatric disorders. But, in reality we are left stranded with bunch of research reports mostly reproving and strengthening earlier theories and hypothesis respectively. There is as yet no definitive and unambiguous evidence that any psychiatric brain imaging measure can provide a comprehensive and clearly incremental improvement to the existent approach to the treatment or even diagnosis of psychiatric illness. Does a pattern of imaging findings reflect a diagnostic entity or is it peculiar to a particular symptom profile? Does inconsistency within a diagnostic or symptom based grouping reflect state related psychological phenomena, or underlying etiological differences, perhaps seen at the level of the genotype? Clearly, the difficulties are highly complex and will not be addressed by any single approach to experimental design but rather by the accumulation of data sets in which the correlations of brain activity with

phenotypic and genotypic variables are examined. It has been possible, for example, to combine functional imaging with molecular genetics and developmental neurobiology. Such an approach, capitalizing on the identification of specific genetic mutations and co-occurring behavioural deficits, may offer the precision that imaging studies require. This evolving alliance along with cognitive neuroscience may in near future identifies neural networks and heralds a new era of knowledge about healthy brain function, the mechanism of disease, underlying etiology, unimagined innovations in therapeutic intervention and efficacious strategies for prevention.

Future directions

- To employ tasks on which performance of the patient and control group is matched, correlation studies should be hypothesis driven. It would be an improvement if a hypothesis are made, based on past data. For example, temporal lobe abnormality might contribute to auditory hallucination because temporal lobe epileptics experience such symptoms.
- Longitudinal investigation could help to resolve whether neuro-pathological changes are related to neuro-developmental or neuro-degenerative process, or an interaction of the two. Investigations with children and younger populations will be necessary
 - To confirm neuro-developmental theories and to demonstrate interactions with normal developmental processes.
 - To consider the need to obtain information about baseline or resting state of human brain.
 - To extend future studies beyond the receptor and neurotransmitter to look into second messenger system in the brain.
 - Application of synergistic approach i.e. using different neuro-imaging modalities complementarily to get more rewarding information to unravel the major issues in clinical neuroscience
 - To integrate regional brain activity data with knowledge of underlying pharmacological mechanisms.

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