Neuroimaging research to the understanding of psychopathology psychology essay

Over the last ten years, neuroimaging techniques has been employed to an ever increasing extent in the investigation of the biological substrates of psychopathology (Malhi and Lagopoulos 2008). Non-invasive brain imaging techniques such as PET and fMRI have been successfully applied in the localization of sensory functions (van Eijsden et al. 2009). For more complex psychological processes such as language, fMRI is now used to guide surgical decisions regarding hemispheric dominance in patients with refractory epilepsy (van Eijsden et al. 2009). Although still in its infancy (Crowe and Blair 2008), neuroimagings existing contribution has been hailed as significant (Linden 2008, Radaelli et al. 2008).

Reliable biomarkers are not known for most, if not all psychiatric disorders (Linden 2008). Limited knowledge concerning the aetiological mechanisms underlying disorders thwart efforts at primary prevention and hamper secondary prevention due to the lack of reliable, comprehensive prognostic markers (Glahn et al. 2008). The lack of pathognomic neural markers, difficulties achieving clinical consensus regarding diagnostic definitions and symptom heterogeneity within the existing diagnostic entities have encouraged neuroimagings pursuit of biomarkers and endophenotypes (Malhi and Lagopoulos 2008); (Pan et al. 2009). The research agenda for DSM V underscores this theme working towards an aetiological and pathophysiological based diagnostic system rather than the current symptom and syndrome based approach (Pan et al. 2009). Neuroimagings contribution may be through refining, validating and augmenting existing diagnostic classifications or replacement of the existing phenomenologically derived system with neuroanatomically defined biomarkers (Malhi and

Lagopoulos 2008). Neuroimagings contribution may be constrained by limited knowledge regarding interregional connectivity and interactions within the brain (Honey et al. 2002). Furthermore, the pathways by which genetic and environmental risk factors interact and impinge upon behaviour ultimately manifesting as pathological symptoms is largely unknown (Glahn et al. 2008). Complexity is increased further by consideration of the points of discontinuity between psychopathology and normal variation (Glahn et al. 2008).

To date, the majority of neuroimaging research has attempted to correlate functional, structural and chemical abnormalities of the brain with the presence and/or severity of symptoms (Radaelli et al. 2008). Critics argue that neuroimaging research encourages a “ segregationist” approach to psychopathology, attempting to map complex functions onto discrete, localized brain areas (Honey et al. 2002). This tendency has been influenced by assumptions within cognitive psychology (van Eijsden et al. 2009), namely that mental functions are comprised of modules with identifiable, specific cognitive content processed by a computer like brain (van Eijsden et al. 2009). Thus, elements of psychological function are assumed to activate specific, reproducible brain regions, a model known as “ massive modularity”(van Eijsden et al. 2009).

Traditionally, neuroimaging techniques have been categorized according to their data acquisition methodology, focusing upon structure, function, connectivity, electrophysiology or underlying chemistry (Pine 2006). Recent advancements in multimodal imaging (MMI) enables an admixture of approaches attempting to integrate the strengths of different techniques

(Malhi and Lagopoulos 2008). Rather than detecting actual neural transmission, fMRI relies on the paramagnetic properties of deoxyhaemoglobin, providing an indirect measurement of the coupling between neural activity and blood flow (Malhi and Lagopoulos 2008). Similarly, PET is an indirect measurement of neural activity measuring blood flow, metabolism or ligand-receptor interactions of particular neurotransmitters (Zimmer 2009). Compared with SPECT, PET offers increased spatial and temporal resolution and permits imaging of a greater range of brain activity than SPECT tracers (Malhi and Lagopoulos 2008). However, it does not offer equivalent spatial resolution to fMRI. DTI tractography images neural tract trajectories, enabling the modelling of white matter fibres localization, orientation, connectivity and integrity within the brain (Malhi and Lagopoulos 2008); (Honey et al. 2002); (Thai et al. 2009).

Neuroimaging research can adopt either a whole brain or region of interest (ROI) approach (Malhi and Lagopoulos 2008) with important implications for interpretation. As ROI approaches examine fewer brain regions than whole brain univariate approaches such as VBM, they offer increased statistical power with a concomitant decrease in explanatory power (Ecker et al. 2010). In contrast, techniques such as VBM offer increased explanatory and moderate statistical power due to the necessity of multiple comparison corrections. Therefore, mass univariate approaches may be too conservative to detect subtle neuroanatomical abnormalities particularly with small samples (Ecker et al. 2010). Additionally, neuroimaging studies can be contrasted in terms of experimental design ranging from block, factorial to

the most recently developed event-related designs. Event-related designs permit randomization of experimental conditions throughout scanning (Honey et al. 2002), allowing the response to a single event to be examined in a context-independent manner (Friston et al. 1998).

This paper will evaluate the possible applications of neuroimaging research to the understanding of psychopathology in terms of its existing contribution and developments which may arise due to further technological innovations in the future. Initially, it will provide a brief introduction to a number of methodological considerations associated with neuroimaging research. Following this discussion, it will primarily focus upon neuroimagings contribution to aetiological research of psychopathology. In addition, it will evaluate the application of neuroimaging techniques to diagnosis, prognostic considerations and treatment. The paper will conclude with a review of recent technological developments within neuroimaging and evaluate the extent to which these innovations may further increase neuroimagings application to the understanding of psychopathology.

Methodological and Technological considerations

Critiques of neuroimaging research as “ The New Phrenology” in its attempts to locate complex psychological phenomena in discrete brain regions have been described as the localization fallacy. The complexity of conducting research with patient groups and interpretation of associated results is emphasised when patient characteristics are considered (Honey et al. 2002). Psychiatric conditions are heterogenous in their presentation and difficult to define as discrete and homogenous entities. This increases the difficulty in

obtaining a clinically homogenous sample for research purposes. Disorder and symptom heterogeneity manifesting as inconsistent neuroimaging findings may be a result of different aetiological pathways, variability in compensatory processes, chronicity of illness or the patients unique symptom profile (Honey et al. 2002). These inherent difficulties have been demonstrated by conflicting findings of hypofrontality in Schizophrenia (Keshavan et al. 2008) and led to the following conclusion “ as long as we are not able to disentangle the heterogeneity question at the clinical level, it is not likely that heterogeneity at the aetiological and pathophysiological levels can be resolved” (Peralta and Cuesta 2000). If a well matched sample is obtained, their symptomatic profile may be a manifestation of the final common pathway of disorder rather than representing a group matched for common aetiological mechanisms (Honey et al. 2002). To counteract these issues, many neuroimaging studies have adopted a symptom level approach, for example exclusively examining AVH (Honey et al. 2002). Critics have argued that symptom provocation studies may be imaging interference processes, compensation for diminished performance or other co-occuring symptoms (Honey et al. 2002). If the assumption that symptoms occur in isolation is correct, their location within discrete brain regions may over overly simplistic, it is more likely they are an element of complex, dynamic neural activity (Honey et al. 2002). The phenomenon of “ pure insertion” asserts that a phenomenon of interest can be identified or manipulated in isolation from other mental processes (Honey et al. 2002). For example, linear increases in cognitive load (task demand) may not be associated with linear increases in neural activity. Furthermore, is it conceivable that ruminations in OCD can be isolated from other processes such as memory,

attention and speech? (Honey et al. 2002). The subtraction technique is the most commonly employed method to identify brain areas that are active relative to one another; therefore, experimental task pairs should only differ in terms of one parameter. This is based on the assumption that by changing one parameter, that only one aspect of processing is altered (Nair 2005).

Neuroimaging results may thus be misinterpreted as the cause of disorder or the disorder itself (Fuchs 2006). Thus, there are a number of important issues to consider when interpreting neuroimaging results such as whether differences reflect a symptom profile, a diagnostic entity and whether differences within these groups relate to state related phenomena or underlying aetiological differences at the genotype level (Honey et al. 2002). These ambiguities have led some researchers to question neuroimagings utility to aetiological research advocating a focus upon diagnostic imaging (Honey et al. 2002). Recent shifts towards a focus upon systems level, dynamic connectivity within the brain appears to be counteracting neuroimagings characterisation as the new phrenology (Zhou et al. 2009).

The complexity of neuronal function has important implications for the analysis and interpretation of neuroimaging results. It is necessary to quantify both the relationship between neuronal activity and indirect measures of it via the haemodynamic responses and the associated temporal delay (Honey et al. 2002). It has been shown that BOLD signals are more responsive to increases rather than decreases in blood flow, known as the haemodynamic rectification effect (Keri and Gulyas 2003). These matters become increasingly complex when the contribution of neurotransmitter release and reuptake, receptor binding and electrical activity to rCBF,

metabolic changes and behaviour are considered (Keri and Gulyas 2003). For example, low levels of neuronal activity may not be accompanied by rCBF changes, in a PET experiment, the lack of activation in this area does not exclude the area from being involved in the response under examination (Keri and Gulyas 2003). In contrast to sustained stimulation, rapid changes in the brains functional state result in a brief uncoupling of perfusion from oxidative metabolism (Keri and Gulyas 2003). Imaging procedures must also model the effect of major blood vessels draining activated brain regions (Honey et al. 2002). Existing technology does not offer equivalent spatial resolution across the whole brain, there are also inherent difficulties differentiating between excitatory and inhibitory activation when using the proxy of the haemodynamic response (Honey et al. 2002). The complexity is further increased when the impact of experimental design is considered. fMRI images particularly those based on block designs frequently are static representations of haemodynamic activity averaged over time (Nair 2005). Furthermore, activity in some regions may only be detectable with more sophisticated event-related rather than block designs (Fusar-Poli et al. 2007). However, it has been shown that even in event-related fMRI paradigms that short interstimulus intervals result in an overlap of haemodynamic responses to individual events (Ecker et al. 2008), thereby precluding confident analysis of condition specific activity. It has also been demonstrated that path co-efficients within SEM fMRI reflect changes in the temporal characteristics of the HFR induced by experimental design (Ecker et al. 2008) emphasising the effect of experimental design on effective connectivity studies.

Recent developments

In recent years there has been increased interest in furthering understanding of interactions between brain regions known as connectivity analysis (Sato et al. 2009b). Functional connectivity refers to the dynamic relationships between brain regions typically based upon correlational analyses (Thai et al. 2009). Effective connectivity studies infer causal or modulatory relationships between brain regions or networks and their directional, temporal interactions (Thai et al. 2009). SEM and DCM are the most commonly employed methods to investigate connectivity within fMRI data (Sato et al. 2009b). In SEM, the strength of an interaction is provided by a path co-efficient measuring the average influence of one ROI on another in a specified time period (Ecker et al. 2008). For example, using effective connectivity, it was demonstrated that the sACC and pACC had a strong directional influence on the right amygdale during an emotional processing task (Zhou et al. 2009). Rather than occurring as functionally distinct, feedforward sequential processing stages, it was shown that mental rotation performance includes both feedforward and feedback connections with indirect evidence of parallel processing (Ecker et al. 2008).

Machine learning and pattern recognition methodologies, such as SVM are powerful techniques for the classification and prediction of mental states so called brain reading or decoding (Sato et al. 2009a); (Sato et al. 2009a). SVMs are used to identify statistical properties of imaging data which discriminate between groups of participants or brain states (Sato et al. 2009b), essentially, whether a new observation belongs to a training data set or otherwise. Not only do they offer the potential to categorize, their ability

to anatomically localize discriminative information generated by the classification process presents the possibility of brain mapping (Sato et al. 2009a). Potentially, this methodology could be used to describe a healthy population, measuring the distance of subsequently tested participants from normative fMRI data (Sato et al. 2009b). For example, SVMs ability to distinguish between visual and auditory stimulation was 95. 34% +/- 18. 77 (Sato et al. 2009a). ANN and SVM based tools have employed in the identification and classification of pathology of patients with Alzheimers or Parkinsons disease from control participants (Bose et al. 2008).

The development of imaging genetics offers the possibility of mapping the biological pathways and mechanisms whereby individual differences in brain function emerge and potentially predispose individuals to risk of psychological dysfunction (Viding et al. 2006). It enables the evaluation of the functional impact of brain relevant genetic polymorphisms with a view to understanding their impact on behaviour (Viding et al. 2006). For example, studies of healthy adult 5-HTTLPR S allele carriers found increased amygdala activation, reduced grey matter volume of the perigenual ACC and amygdale and altered functional connectivity of the pACC and amygdale relative to the LL genotype. Furthermore, 30% of variance in behavioural harm avoidance scores during this fMRI challenge paradigm was predicted by amygdala – pACC functional connectivity (Viding et al. 2006).

Aetiology

Significant ambiguity remains surrounding the pathogenesis of schizophrenia (Keshavan et al. 2008). Although the majority of psychological disorders are

thought to be multifactorial in origin (Glahn et al. 2008), genetic factors appear to exert a significant aetiological influence on the major psychoses, twin studies estimating heritability at 80% (van Os and Kapur 2009). Structural MRI studies have revealed reductions in whole brain and grey matter volume as well as increases in ventricular volume (Keshavan et al. 2008; van Os and Kapur 2009). Reductions have been observed in temporal lobe structures (in particular the hippocampus, amygdala and the superior temporal gyrus) and the prefrontal cortex, thalamus, AC and corpus callosum. There is evidence of a relationship between superior temporal gyrus volume and positive symptoms; medial temporal lobe reductions correlating with memory impairment. Qualitatively similar but less marked structural changes have been observed in the affective disorders. Whilst structural abnormalities may be consistently found in Schizophrenia, they are diagnostically non-specific and may be common amongst patients across diagnostic classifications. Evidence of progressive brain changes during the course of schizophrenia suggests that structural abnormalities may be a result of early and later developmental dysfunction (Karlsgodt et al. 2008). The onset of frank symptoms has been associated with progressive changes. Using longitudinal research designs, deviations from normative development can be examined (Serene et al. 2007). For example, longitudinal studies of early onset schizophrenia demonstrated progressive grey matter loss across the lateral surface of the brain, with treatment refractory patients displaying the most pronounced and rapid cortical grey matter loss. However, the explanatory power of progressive brain structural changes as the primary pathophysiological process within schizophrenia is diminished due to the presence of potentially confounding factors secondary to the illness such as

symptom profile, severity, medication history and status and the duration of illness (Karlsgodt et al. 2008). Furthermore, structural changes are generally subtle and of relatively small effect sizes (Keshavan et al. 2008).

Inconsistency has mired findings of hypofrontality in Schizophrenia, functional imaging meta-analysis have calculated moderate effect sizes for activated and resting state conditions. Conversely, once performance differences are controlled for, patients have shown increased prefrontal activation relative to controls perhaps indicative of an inefficient frontal response to task demands. There have been similarly inconsistent findings regarding other brain regions. Functional imaging research has found alterations in prefrontal and occasionally temporal lobe function (Shergill et al. 2007), with speculation regarding a specific abnormality in the reciprocal modulatory interaction of frontal areas and the hippocampus (van Os and Kapur 2009). Hyper- and hypoactive network responses have been demonstrated depending on experimental paradigm (van Os and Kapur 2009). Inconsistencies in the functional imaging literature may be a result of the diverse experimental designs employed, non-uniform standardization of resting state conditions, lack of control for performance differences, typically small sample sizes and medication confounds which curtail the interpretability of these results (Keshavan et al. 2008). MRS studies have corroborated regions implicated by structural and functional imaging results demonstrating reductions in neuronal and membrane integrity in at risk and early schizophrenic groups. However, it can be concluded that many of schizophrenias putative biomarkers are of less than robust effect sizes, non-specific and too time consuming or expensive to consider implementing as

potential diagnostic biomarkers (Keshavan et al. 2008). It is proving difficult if not impossible to explain the features of this disorder and its associated functional deficits in terms of selective, focal abnormalities (Fusar-Poli et al. 2007).

The disconnectivity hypothesis of the pathophysiological basis of vulnerability to psychosis implicates abnormal interaction/disconnectivity of the prefrontal cortex, temporal lobe and subcortical regions (Fusar-Poli et al. 2007). Findings of disturbed functional connectivity of the medial prefrontal, thalamic and cerebellar regions in relatives of patients with schizophrenia have provided support for this view (Fusar-Poli et al. 2007). Although evidence for disconnectivity in schizophrenia is strong, its relationship to aetiology, pathophysiology and implications for symptomatic behaviour remain unclear (Stephan et al. 2009).

AVH have been found to activate a wide network of language areas in the frontal and temporal lobes and limbic areas such as the amygdale and hippocampus (Vercammen et al. 2009). The subjective intensity of AVH has been correlated with activation of the primary auditory cortex. Schizophrenic patients who experience AVH have been found to activate differential brain areas relative to healthy controls and non-hallucinating patients with schizophrenia, displaying altered activation of the anterior cingulate and superior temporal regions bilaterally (Mechelli et al. 2007; Shergill et al. 2007). DTI studies have demonstrated differences in the orientation of white matter fibres relative to patients without AVH and healthy controls. Examining the effective connectivity of AVH using DCM demonstrated a specific impairment of functional integration between the left superior

temporal cortex and the dorsal part of the ACC during the evaluation of self and alien generated speech in patients with AVH (Mechelli et al. 2007). This implies a relationship between impaired functional integration and AVH experiences, Mechelli et al, speculate that a similar impairment in effective connectivity may diminish patients ability to process their own inner speech. Furthermore, a whole brain DTI study illustrated that propensity to experience AVH was associated with increased fractional anisotrophy (FA) within lateral aspects of the superior longitudinal fasciculi bilaterally, the main connection area between Wernicke's and Broca's areas (Shergill et al. 2007). Similar differences in FA have been reported in at risk and first episode patients. However, it is possible that these connectivity changes may be a result of experiencing AVH rather than being causative in nature. Increased frequency of AVH may enhance connectivity in these regions.

Studies conducted during the prodromal phase permit the prospective investigation of the pathophysiological processes underlying vulnerability and development of the disorder (Fusar-Poli et al. 2009; Pantelis et al. 2003). Neuroimaging studies have demonstrated qualitatively similar abnormalities to those evident in established schizophrenia and bipolar to those present in first episode psychosis and individuals without psychosis but with a strong familial risk (Pantelis et al. 2003). At risk individuals who subsequently developed psychosis had smaller grey matter volumes in the right medial temporal region, including the hippocampus and parahippocampal cortex, in a right lateral temporal region encompassing the superior temporal gyrus, a right inferior frontal region including the orbital portion of the inferior frontal gyrus and adjacent parts of the insula and basal ganglia and a cingulate

region including the anterior and posterior cingulate gyrus bilaterally which mimics findings in probands of MZ twin pairs discordant for schizophrenia, first degree relatives of patients with psychosis and people with schizotypal personality disorder. Longitudinal examination of patients who transitioned to psychosis, showed a significant bilateral reduction in grey matter volume between baseline and follow up in the cingulate gyri, the left parahippocampal gyrus, left fusiform gyrus and left OFC (Pantelis et al. 2003). This study demonstrated that pathophysiological anomalies predate the onset of overt psychosis but that further grey matter volume changes are associated with the first expression of frank symptoms. It is unclear however, whether these changes represent a cause or effect of psychosis. Pantelis et al conclude that MRI may in the future prove a valuable tool in the identification of ultra high risk individuals.

Neurochemical PET and SPECT studies investigating the dopamine hypothesis of schizophrenia with 18 F-dopa and 11 C-raclopride have shown that schizophrenia in its acute psychotic state is associated with an increase in dopamine synthesis, dopamine release and resting state dopamine concentration (van Os and Kapur 2009). Research has also demonstrated pre-synaptic dopamine overactivity in schizophrenic patients and first episode patients (Fusar-Poli et al. 2009)

Studies of prodromal patients have demonstrated elevated Striatal 18 F-dopa uptake with levels approaching those of Schizophrenic patients (Howes et al. 2009). 18 F-dopa uptake in the ARMS was directly correlated with symptom severity and the degree of neuropsychological impairment. The most pronounced dopaminergic abnormality was found in the associative

subdivision of the striatum in both schizophrenic patients and individuals with an at risk mental state (Howes et al. 2009). Thus, it has been suggested that pre-synaptic striatal dopamine function may be a worthwhile target for novel drug development and that these findings may provide a neurophysiological rationale for the introduction of anti-dopaminergic preventative intervention in high risk individuals (Howes et al. 2009).

Multimodal studies of a verbal fluency task during the ARMS demonstrated an association between altered prefrontal activation and striatal hyperdopimergia (Fusar-Poli et al. 2009). Controlling for performance differences, there was increased activation of the left inferior frontal gyrus and the right middle frontal gyrus suggesting reduced efficiency or a compensatory process to achieve a similar behavioural response as controls. Improvement in prodromal symptoms has been associated with a normalization of the exaggerated inferior frontal response during a verbal fluency task. Previous findings linking the degree of elevation of striatal hyperdopimergia with symptom severity suggest that striatal hyperdopaminergia may underlie both symptoms and neurocognitive dysfunction although it is possible that another pathway is responsible. The observed correlation may represent the effect of prefrontal cortex on striatal dopamine or vice versa. Crucially, this study demonstrates that abnormalities which were heretofore regarded as key pathophysiological features of Schizophrenia are correlates of vulnerability rather than sufficient for development of the disorder (Fusar-Poli et al. 2009).

Interpretation of ARMS findings is difficult due to uncertainty regarding the degree to which they reflect trait or state factors, that is, psychosis liability or prodromal symptoms (Fusar-Poli et al. 2007).

Thus, neuroimaging findings indicate changes in gray matter structure indicative of connectivity deficits at the level of synaptic connections and neuropil allied with white matter changes indicative of large scale deficits in connections between cortical regions (Karlsgodt et al. 2008). Although several biological abnormalities have been replicated (abnormally large ventricles, abnormal dopamine concentration and altered P300) they are not sensitive enough (usually only seen in 40-50% of patients) or not specific enough (seen in only 30% of first degree relatives) to be of diagnostic influence (van Os and Kapur 2009).

Anxiety Disorders

Neuroimaging research of anxiety disorders have implicated brain areas involved in the stress response as being associated with anxiety symptoms, including the prefrontal cortex, hippocampus and amygdala (Engel et al. 2009). However, potential brain structures implicated in the pathophysiology of anxiety disorders are extremely difficult to image due to their sizes and locations these include the amydala, brainstem nuclei and periaquaductal gray (Engel et al. 2009). Neuroimaging of PTSD highlights many of the complexities involved in conducting this research. Complexities relate to symptom presentation in terms of their variable content and emotional arousal in particular during the retrieval of traumatic memories (Peres et al. 2008). Symptomatic heterogeneity is extremely difficult to control for, additional potential confounds include nature of the traumatic experience (s)

and the length of time since its occurrence. It is questionable whether it is appropriate to generalize from imaging results based on a sample of war veterans to survivors of childhood abuse (Peres et al. 2008). However, the results of neuroimaging studies appear to offer support for two broad subtypes of PTSD, one being primarily dissociative, the other characterised by intrusions and hyperarousal (Malhi and Lagopoulos 2008). Structural studies have demonstrated reduced ACC and hippocampal volumes in studies across a variety of traumatic experiences. Increased amydala activation has also been observed (Crowe and Blair 2008). Impaired hippocampal function has been speculatively linked to the memory fragmentation process observed in PTSD (Peres et al. 2008). However consistent findings of structural or functional change, they do not necessarily imply a causative relationship.

Depression

Research investigating the pathophysiology of depression have highlighted decreased anterior paralimbic and cortical activity in both major and bipolar depression (Malhi and Lagopoulos 2008). These decreased activation patterns are found to reverse with successful treatment. For example, in studies of major depression it has been observed that diminished activation of the dorsalateral prefrontal cortex can be increased following effective treatment. PET studies of the serotonin transporter SERT have demonstrated increased thalamic SERT in depressed patients relative to controls. Across the affective disorders, findings of hyperamydala and hypofrontality have led to speculation that these abnormalities may represent a critical pathway or potential predictive biomarker for those at risk of future development of

psychopathology (Viding et al. 2006). However, it remains unclear as to whether these findings represent state or trait related function. The search for trait related biomarkers offers the potential to uncover early warning signs of impending psychological disorder as they may be present prior to symptom onset (Malhi and Lagopoulos 2008). The clarification of state related changes affords the possibility of monitoring differential responses to treatment over time (Malhi and Lagopoulos 2008). Cautious interpretation of existing neuroimaging findings is advised due to the complexity of emotional networks and lack of understanding regarding their integration with higher cognitive processes (Malhi and Lagopoulos 2008).

Diagnosis

As of yet there are a limited number of neuroimaging studies attempting to classify or categorize disorder (Glahn et al. 2008). Ongoing research endeavours to uncover pathophysiological biomarkers complements the development of diagnostic imaging systems.

The discovery of biomarkers of schizophrenia may assist in early diagnosis and haveprognostic value (Bose et al. 2008). Initial diagnostic research efforts focused on measurement of striatal D2 receptor levels. Although it appears that striatal D2 receptor levels are elevated in schizophrenia, inconsistent and variable PET and SPECT results (possibly related to samples tested) have precluded its use as a diagnostic variable (Bose et al. 2008). Machine learning and pattern recognition techniques provide methods for analysing imaging data that may improve the sensitivity and specificity of diagnosis (Bose et al. 2008). Using ANN modelling of striatal [18F] fluro-L-

DOPA influx constants, it was found that an ANN model correctly classified 84% of schizophrenic patients and 74% of controls (Bose et al. 2008). Sensitivity analysis revealed that the posterior putamen and anterior caudate nucleus were the most important areas within the ANN classification. The addition of multiple risk factors to the ANN classifier such as neuropsychological, genetic or structural imaging results may improve the ANN classifiers accuracy further (Bose et al. 2008). Bose et al, 2008 suggest the potential util