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The Use of 31-Phosphorus Magnetic Resonance Spectroscopy to Study Brain Cell Membrane Motion-Restricted Phospholipids

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1. Introduction

Until relatively recently, the only way non-invasively to study brain cell membrane phospholipids in humans *in vivo* has been through the quantification of membrane phospholipid metabolism by means of ascertaining the levels of phosphomonoesters and phosphodiesters from 31-phosphorus neurospectroscopy scans. However, this only gives an indirect measure of the cell membrane phospholipid molecules. Ideally, one would want to study the brain cell membrane motion-restricted phospholipids directly, but it has previously proved almost impossible to obtain high-resolution magnetic resonance spectra of membrane phospholipids in living tissues owing to the large chemical-shift anisotropy of the 31-phosphorus confined to what is, in terms of nuclear magnetic resonance, the relatively rigid structure of the cell membrane, whether this be the external cell membrane or the membrane of an intracellular organelle.

2. 31-Phosphorus neurospectroscopy

Since structural imaging depends on the measurement of proton-based resonances, proton neurospectroscopy is readily achievable, in terms of hardware requirements, from magnetic resonance imaging scanners that are used for structural neuroimaging studies in humans. In contrast, the excitation of 31-phosphorus-containing relatively free moieties from the human brain and the measurement of the corresponding 31-phosphorus signals from relaxation of the 31-phosphorus nuclei require the use of a different coil tuned to the resonance frequency corresponding to the latter nuclei. The resonance frequency, ω, depends also on the strength of the static magnetic field, B_0, and is given by the Lamor equation:

$$\omega = \gamma B_0 \tag{1}$$

where γ refers to the gyromagnetic constant (or ratio) and is the ratio of the nuclear magnetic moment to the nuclear spin angular momentum. The gyromagnetic constant has a

unique value for each nuclide possessing a nuclear magnetic moment, such as 31-phosphorus. For example, the value of the gyromagnetic constant for 31-phosphorus is 17.23 MHz T^{-1} while for the proton (1-hydrogen) it is 42.58 MHz T^{-1}. Hence, at a value of B_0 of 1.5 T, which is common for many magnetic resonance scanners in clinical use at the time of writing, whereas the value of the resonance frequency is 63.87 MHz for protons, it is just under 26 MHz for 31-phosphorus. A method our group have used to allow us to carry out 31-phosphorus neurospectroscopy studies without having to move each subject's head in relation to the magnetic resonance scanner, is to employ a birdcage quadrature head coil dual-tuned to proton (64 MHz) and 31-phosphorus (26 MHz); the proton tuned coil is required to enable T_1-weighted structural scans to be obtained, in order to allow subsequent spectral localization (Puri et al., 2008b).

Conventional 31-phosphorus neurospectroscopy allows us readily to discern seven narrow resonances from the adult human brain. In decreasing order of chemical shift, these are signals from phosphomonoesters, inorganic phosphate, phosphodiesters, phosphocreatine, gamma nucleotide triphosphate, alpha nucleotide triphosphate, and beta nucleotide triphosphate. The first and third narrow resonances, corresponding to phosphomonoesters and phosphodiesters, respectively, are considered further below.

2.1 Phosphomonoesters and phosphodiesters

The 31-phosphorus neurospectroscopy narrow resonances corresponding to phosphomonoesters and phosphodiesters are important in respect of membrane phospholipid metabolism for the following reasons.

The phosphomonoesters narrow resonance reflects membrane phospholipid anabolism. This is because it contains contributions from freely mobile phosphomonoesters, including phosphocholine, phosphoethanolamine, and even small contributions from inositol phosphate, glycerophosphate, phosphothreonine, and *L*-phosphoserine, and also contributions from less mobile phosphomonoester-containing molecules, such as certain phosphorylated proteins, and from certain proteins that are part of the neuronal cytoskeleton (Puri, 2006).

In contrast, the phosphodiesters narrow resonance reflects membrane phospholipid catabolism, since it contains contributions from freely mobile phosphodiesters, including glycerophosphocholine and glycerophosphoethanolamine. The phosphodiesters narrow resonance also contains contributions from less mobile phosphodiester-containing molecules, such as molecules involved in membrane structure (both cell membranes and intracellular organelle membranes) (Puri, 2006).

Traditionally, therefore, the ratio of phosphomonoesters to phosphodiesters has been used as an index of membrane phospholipid metabolism. We turn next to a consideration of the presence of a broad component in the 31-phosphorus neurospectroscopy spectrum, which enables brain cell membrane motion-restricted phospholipids to be assessed more directly than a consideration of just phosphomonoesters and phosphodiesters.

2.2 Broad component

In explaining the advantages of measuring the broad component in the 31-phosphorus neurospectroscopy signal, the reader may be struck by what is in retrospect a rather ironic fact that for many years this broad component has been treated as somewhat of a nuisance,

with attempts being made to eliminate it altogether, as far as possible, from the final spectral analysis (Estilaei et al., 2001). For example, in previous neurospectroscopy research studies, our group have often used a fully automated approach to minimize the baseline roll in chemical shift imaging using a technique that employed knowledge-based data processing in the frequency domain, the broad component being regarded as an artefact that appeared as a result of the summation of several sinc functions; using prior knowledge, a mirror component corresponding to the 'artefact' was created and added to the delayed spectrum and this method compensated for noise and zero-order phase error when computing the roll artefact (Saeed and Menon, 1993).

The broad resonance which underlies the 31-phosphorus spectrum from the living mammalian brain is composed of signal directly from the cell membrane phospholipids (Hamilton et al., 2003a). Thus the quantification of this broad resonance from 31-phosphorus neurospectroscopy data provides a more direct measure of brain cell membrane motion-restricted phospholipids than does the evaluation of the ratio of phosphomonoesters, which index phospholipid anabolism, to phosphodiesters, which index phospholipid catabolism. The convolution difference resolution enhancement method may be used to obtain the broad component integral, from spectra obtained using an image-selected *in vivo* spectroscopy sequence (ISIS) (Estilaei et al., 2001, Roth and Kimber, 1982), whereby the broad component is the difference between the measured raw signal intensity, S, and S_{CD} given by:

$$S_{CD} = S(1 - fe^{-\pi Lt}) \tag{2}$$

where f is the convolution-difference factor, representing the fraction of the broad component contributing to the acquired signal at a given echo time (TE), and L is an exponential filter; the broad component integral may then found by fitting the broad spectrum to multiple Gaussian lines, minimizing residuals, and summating over all Gaussian-line integrals. Estilaei and colleagues (2001) obtained transverse relaxation time (T_2)-magnetization decay curves by plotting the broad component area as a function of TE; having found that mono-exponential fitting did not adequately represent T_2-magnetization decay curves, they instead used the following bi-exponential fit:

$$S(t) = S_l\, e^{-A} + S_s\, e^{-B} \tag{3}$$

where $S(t)$ is the total magnetization at a given time t, S_l and S_s are the respective equilibrium magnetizations for the slow and fast decaying components, A is the quotient of the echo time and the spin-spin relaxation time for the long T_2 component, T_{2l} , and B is the quotient of the echo time and the spin-spin relaxation time for the short T_2 component, T_{2s}. Using the model of Radda's group in which T_{2l} is much greater than T_{2s} (Kilby et al., 1990), Estilaei and colleagues (2001) showed that the uncertainty in the determination of the long T_2 could be eliminated, and, with TE much less than T_{2l}, it followed that

$$\ln S(TE) = \ln (S_l + S_s) - S_s\, TE/(\, T_{2s}\, (S_l + S_s)) \tag{4}$$

and, with TE much greater than T_{2s}

$$\ln S(TE) \simeq \ln S_l - TE/T_{2l} \tag{5}$$

Linear regression was then used to carry out the corresponding fits.
Our group have tended to quantify the 31-phosphorus signals using prior knowledge in the temporal domain using the AMARES (advanced method for accurate, robust, and efficient spectral fitting) algorithm (Vanhamme et al., 1997) included in the Java-based MRUI (magnetic resonance user interface) software program, which allows time-domain analysis to be easily carried out (Naressi et al., 2001). Truncation of a specific early portion of the signal removes the broad component present in the 31-phosphorus spectra and allows initial analysis of the narrow components listed above using *a priori* knowledge in the AMARES algorithm (Hamilton et al., 2003a, Hamilton et al., 2003b). The broad hump can then be analyzed, using the above time-domain analysis, thereby allowing distinct separation of the narrow and broad components. The broad component is modelled as a Gaussian function and its area can be compared with the total peak area of the seven narrow resonances and then multiplied by 100 to give the percentage broad signal (Puri et al., 2008b).

2.3 Chronic alcohol consumption

It has been shown that ethanol increases the fluidity of spin-labelled membranes from normal mice, while membranes from mice that have been subjected to long-term ethanol treatment are relatively resistant to this fluidizing effect and have an altered phospholipid composition; this suggests that the membranes themselves had adapted to the alcohol, which constitutes a novel form of drug tolerance (Chin and Goldstein, 1977). This finding from this landmark 1977 study has been replicated using non- nuclear magnetic resonance techniques, including electron spin resonance and fluorescence polarization: chronic alcohol exposure in humans increases the rigidity of isolated brain membranes.
The related hypothesis that subjects who are heavy drinkers have stiffer brain cell membranes than have control subjects who are light drinkers, as reflected in a smaller broad signal component with a shorter T_2 of the broad signal from 31-phosphorus neurospectroscopy, was tested by Estilaei and colleagues (2001). They carried out localized 31-phosphorus neurospectroscopy at the level of the centrum ovale in 13 male alcohol-dependent heavy drinkers of average age 44 years (standard deviation 9 years) who had an average lifetime alcohol consumption of 239 (standard deviation 218) drinks per month, where one drink was taken to be an alcoholic beverage containing approximately 13 g ethanol, and who satisfied the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria for lifetime dependence on alcohol (American Psychiatric Association, 1992). Seventeen male non-dependent light drinkers whose average lifetime alcohol consumption was 19 drinks (standard deviation 17 drinks) per month, and whose average age (37; standard deviation 10) years was similar to that of the first group, acted as the control group for this study. The broad component integral was found to be 13 per cent lower in the heavy drinkers compared with the light drinkers ($p = 0.000\ 5$), while no significant differences were found for any of the metabolite integrals. No significant main effect of a family history of alcohol use, assessed using a standard questionnaire, was found, and there was no significant family history-by-group interaction effect on the broad component integral. No significant correlations were found between, on the one hand, the broad component signal integral or its relaxation times, and, on the other hand, age, years of abuse, average monthly drinking or total lifetime consumption in either the heavy drinking group, or the control group or a combination of

both groups. A positive family history of alcohol abuse did not predict a smaller broad component integral or shorter relaxation times (Estilaei et al., 2001). In both the heavy drinkers and the control group, the T_2 distribution of the broad component consistently showed two resolvable components, with the fast relaxing component having the same T_2 in both groups while the slower relaxing component T_2 was 0.6 ms shorter in the heavy drinkers (Estilaei et al., 2001).

The authors concluded that 31-phosphorus neurospectroscopy 'provides a powerful and practical approach for measuring in vivo changes of the amount and fluidity of [phospholipids] in white matter regions of the human brain. Specifically, the smaller, broad component in [heavy drinkers] compared with [light drinkers] suggests altered white matter [phospholipids] associated with long-term chronic alcohol abuse…[and] may provide valuable information regarding possible biochemical mechanisms that [underlie] chronic alcohol-induced structural changes…' (Estilaei et al., 2001).

2.4 Hypoxia resulting from chronic obstructive pulmonary disease

The maintenance of cerebral metabolic homeostasis is required for the maintenance of consciousness and normal brain function, and this may be perturbed by a variety of insults, including hypoxia (Hamilton et al., 2003a). Taylor-Robinson's group at Hammersmith Hospital in London, U.K., had previously shown that abnormal cerebral bioenergetics can be detected readily using 31-phosphorus neurospectroscopy in a study of 10 patients with stable, but severe, chronic obstructive pulmonary disease and hypoxia; compared with controls, the patients with chronic obstructive pulmonary disease showed increased phosphomonoesters and inorganic phosphate signals but reduced phosphodiesters signals, thought to be caused by the utilization of anaerobic metabolism by the brains of hypoxic patients with this disease (Mathur et al., 1999). Since neonatal, animal and *in vitro* studies show an association between anaerobic glycolysis with a protective intracellular alkalosis, the same group attempted to identify such a compensatory intracellular alkalosis in eight hypoxic patients with chronic obstructive pulmonary disease, compared with eight age-matched control subjects, using 31-phosphorus neurospectroscopy (Hamilton et al., 2003a). As part of this study, the broad component was also quantified in the subjects.

Taylor-Robinson's group reported that the mean intracellular pH in patients with chronic obstructive pulmonary disease was similar to that in the control subjects, but decreased in the patients by a mean of 0.02 following the administration of supplemental oxygen, there being no such change in normal control subjects following oxygen administration. Of particular interest was their finding that the broad component increased in all the patients with chronic obstructive pulmonary disease following oxygen administration (Hamilton et al., 2003a). These findings point to altered phospholipid membrane fluidity in the brain being associated with the change in intracellular pH following oxygen administration. The change in the broad resonance was strongly and negatively correlated with the change in intracellular pH, and indeed *in vitro* studies have shown that membrane fluidity is sensitive to pH with, for example, the fusion process between synaptosomes, freshly isolated from rat brain cortex, and large unilamellar phosphatidylserine liposomes being shown to be pH dependent (an increase in both kinetics and extent occurring when the pH is lowered by 1.9 from 7.4) (Almeida et al., 1994).

Based on the above findings, including the results relating to the broad component from 31-phosphorus neurospectroscopy, the authors hypothesized that the transition from compensatory respiratory failure in patients with hypoxic chronic obstructive pulmonary disease to the clinical picture of confusion, disorientation and coma in patients with chronic obstructive pulmonary disease and with severe exacerbations may be associated with the failure of ion transport mechanisms, perturbation of membrane fluidity and the overwhelming of the compensatory intracellular alkalosis in neuronal and glial cells (Hamilton et al., 2003a).

2.5 Schizophrenia

A number of lines of evidence from biochemical studies have suggested that membrane phospholipid metabolism may be impaired in at least a subgroup of patients suffering from schizophrenia (Puri et al., 2008a). First, reduced levels of highly unsaturated (or polyunsaturated) fatty acids have been reported in erythrocyte membranes (Yao and van Kammen, 1994, Yao et al., 1994a, Yao et al., 1994b, Peet et al., 1995) in patients with schizophrenia. Second, increased levels of the phospholipase A_2 group of enzymes, which catalyze the removal of highly unsaturated (or polyunsaturated) fatty acids such as arachidonic acid and docosahexaenoic acid from the Sn2 position of membrane phospholipid molecules, have been found in both plasma (Gattaz, 1992, Gattaz et al., 1990, Gattaz et al., 1987, Tavares et al., 2003) and platelets (Gattaz et al., 1995) of patients with schizophrenia. Furthermore, the dermatological response to the niacin flush test, which indirectly indexes membrane phospholipid metabolism, has been found to be impaired in schizophrenia (Ward et al., 1998), including in its quantitative measurement form as the volumetric niacin response (Puri et al., 2002). These converging lines of evidence are consistent with the membrane phospholipid hypothesis of schizophrenia, associated with the late Professor David F. Horrobin, and also with Professor Iain Glen and Professor Krishna Vaddadi, which proposes a change in brain membrane phospholipids leading in turn to changes in the functioning of membrane-associated proteins and of cell signalling systems in schizophrenia (Horrobin, 1996, Horrobin, 1998, Horrobin et al., 1994).

Clearly, the above biochemical studies have not directly measured membrane phospholipids from the brains of patients suffering from schizophrenia. Similarly, as mentioned earlier, the quantification of the ratio of phosphomonoesters to phosphodiesters, gleaned from narrow resonances obtained from 31-phosphorus neurospectroscopy, also only provide an indirect measure of the ratio of brain cell membrane phospholipid anabolism to phospholipid catabolism. Therefore, there is a clear role for analyzing the broad component from 31-phosphorus neurospectroscopy in schizophrenia. Accordingly, our group were the first to do so.

In our initial study, we carried out the first analysis of the broad component resonance from the brain in forensic patients severely affected with schizophrenia and a comparison group of age- and gender-matched healthy normal control subjects, to assess directly whether, as expected under the membrane phospholipid hypothesis of schizophrenia, there was a change in cell membrane phospholipids in people suffering from schizophrenia who have a forensic history such as having perpetrated an act of serious violence while psychotic (Puri et al., 2008b). Fifteen male inpatients in a medium secure

unit with a diagnosis of schizophrenia according to DSM-IV (American Psychiatric Association, 1992), and 12 male healthy control subjects underwent 31-phosphorus neurospectroscopy. Expert psychiatric opinion, accepted in court, was that all the patients had violently offended directly as a result of schizophrenia prior to admission to the unit, these offences consisting of homicide, attempted murder, or wounding with intent to cause grievous bodily harm. There was no history of alcohol dependency in these patients or in the control subjects. All the patients were suffering from severe positive symptoms of schizophrenia, mostly controlled by antipsychotic medication at the time of scanning. The average duration of illness since the index offence was 6.8 (standard error 0.4) years. Fourteen of the patients were being treated with typical antipsychotic medication, mainly in injectable depot form, while the remaining patient was being treated with clozapine. Spectra were obtained using an image-selected *in vivo* spectroscopy sequence with 64 signal averages localized on a 70 x 70 x 70 cubic millimetre voxel. Owing to the low abundance in the brain, and indeed the rest of the body, of 31-phosphorus compared with protons, the maximum size voxel was used to collect signal from the brain and thus maximize the signal-to-noise ratio. All spectral analyses were carried out by a single observer who was blinded to group allocation until after the spectral and statistical analyses were completed. It was found that the mean percentage broad component signal for the patients did not differ significantly from that for the control subjects and therefore it was not possible to reject the null hypothesis that there is no difference in the concentration of brain membrane-bound phospholipids in this group of forensic patients with schizophrenia compared with controls.

The above finding from analysis of the broad component in forensic patients with schizophrenia was a surprise to our group. An explanation based on the notion that the membrane phospholipid hypothesis applies not only to the outer cell membranes but also to the phospholipid membranes of intracellular organelles such as the nucleus and mitochondrion does not hold since the broad component resonance signal derives from both the outer cell membranes and the phospholipid membranes of these organelles (Puri et al., 2008b).

We carried out a review of the evidence relating to the membrane phospholipid hypothesis of schizophrenia (Puri et al., 2008b). There is strong evidence favouring this hypothesis. As alluded to above, much of this evidence is, as might be expected, primarily biochemical in nature. Plasma phospholipids that have been studied in schizophrenia have tended to show reduced levels of the *n*-6 (or omega-6) fatty acids linoleic acid and arachidonic acid and raised levels of *n*-3 (or omega-3) fatty acids (Horrobin et al., 1989). Interestingly, in a study of plasma phospholipids in patients with schizophrenia, patients with affective and paranoid disorders, and normal controls, from Japan, it was found that while the patients with schizophrenia had low linoleic acid levels (and a low ratio of linoleic acid to its metabolites), and while phospholipid fatty acid levels were in the normal range for the patients with paranoid or affective disorders, those patients with schizophrenia who showed reduced platelet sensitivity to the aggregation-inhibiting effects of prostaglandin E_1 had higher levels of oleic acid and lower levels of eicosapentaenoic acid (Kaiya et al., 1991). This possibility of a dichotomous nature to the fatty acid changes in plasma in schizophrenia also extends to erythrocyte membrane fatty acids.

Erythrocyte membrane fatty acid changes in schizophrenia have been found more consistently than plasma fatty acid changes (Puri et al., 2008b). They tend to point to reduced erythrocyte membrane levels of the long-chain polyunsaturated fatty acids arachidonic acid and docosahexaenoic acid, in the context of a biphasic distribution with one group of schizophrenia patients having essentially normal fatty acid levels, while the other has significantly low levels (Glen et al., 1994). It is of particular interest to note that when the schizophrenia patients were divided into those with predominantly negative symptoms, such as affective flattening, and predominantly positive syndromes, including positive symptoms such as auditory hallucinations and thought disorder, the low erythrocyte membrane levels of arachidonic acid and docosahexaenoic acid were largely confined to patients with a negative syndrome (Horrobin, 2003).

Clearly it was the case that the schizophrenia patients in the above broad component 31-phosphorus neurospectroscopy study would all fit into the category of a positive syndrome, given their history of seriously and violently offending while psychotic (Puri et al., 2008b) . Therefore, this may provide a possible explanation as to why the results of this study did not harmonize with the neurospectroscopy changes expected under the membrane phospholipid hypothesis of Horrobin, Glen and Vaddadi. It was therefore decided to carry to a further study of the broad component from 31-phosphorus neurospectroscopy scanning of patients with schizophrenia, but this time of a sample taken from patients who had not seriously or violently offended as a result of their illness and who suffered from predominantly negative symptoms.

For our new 31-phosphorus neurospectroscopy investigation, our group studied 16 psychiatric outpatients who had a diagnosis of schizophrenia according to DSM-IV (American Psychiatric Association, 1992), who had no history of dependency on psychoactive substances, and the same number of normal healthy controls, who had no previous history of psychiatric or neurological disorders. The two groups were matched with respect to age and gender. The patients suffered from mild to moderate negative symptoms of schizophrenia and had no history of having committed any violent or other offences as a result of their schizophrenic illness. The 31-phosphorus neurospectroscopy protocol was as mentioned above for the forensic schizophrenia study, with spectra being obtained from an image selected *in vivo* spectroscopy sequence with 64 signal averages localized on a 70 x 70 x 70 cubic millimetre voxel, with the signal-to-noise ratio again being improved by using this large voxel size (Puri et al., 2008a).

The broad component from each subject was quantified by an observer who at the time of this analysis was blinded to group status. Just as in our previous study mentioned above, analysis of these broad resonances in this new study showed no significant difference in the broad component between the group of patients with schizophrenia and the normal control group.

We considered that an explanation of these negative results might lie in the possibility that the membrane phospholipid hypothesis of schizophrenia could possibly be construed as predicting a change only in phospholipid metabolism in the cell membranes of the brain, rather than a change in the membrane-bound phospholipids themselves. To test this possibility, a further blinded analysis was carried out of the percentage phosphomonoesters (indexing phospholipid anabolism) and phosphodiesters (indexing phospholipid catabolism) levels in both groups. The mean (standard error) percentage

phosphomonoesters level for the patients with schizophrenia was 11.4 (0.3) and did not differ significantly from that for the normal control subjects of 10.9 (0.5). Similarly, the mean (standard error) percentage phosphodiesters level for the schizophrenia patients was 44.4 (0.5), which did not differ significantly from that for the normal control subjects of 44.6 (0.9) (Puri et al., 2008a). In terms of ratios, the mean ratio of phosphomonoesters to phosphodiesters was 0.26 (standard error 0.01) in the case of the patients with schizophrenia and 0.25 (standard error 0.01) for the healthy controls (Puri et al., 2008a), and again these did not differ significantly. Therefore, on the basis of this second study, it was not possible to reject the null hypothesis that there was no difference in phospholipid metabolism in the brain in the schizophrenia patients compared with the age- and gender-matched control subjects.

Our two sets of 'negative' results in schizophrenia do not, of course, negate the value of quantifying the broad component gleaned from 31-phosphorus neurospectroscopy studies. Rather, they must give us cause to examine again the membrane phospholipid hypothesis of schizophrenia.

3. Conclusion

The above studies of chronic alcohol dependence, chronic obstructive pulmonary disease, forensic inpatients with schizophrenia who have seriously and violently offended while psychotic, and of outpatients with schizophrenia who are suffering from predominantly mild to moderate negative symptoms of schizophrenia, have demonstrated the feasibility of analyzing the broad component from 31-phosphorus neurospectroscopy studies in a wide range of patient groups. We have also shown the advantages over analysis of narrow resonances corresponding to levels of phosphomonoesters (indexing phospholipid anabolism) and phosphodiesters (indexing phospholipid catabolism) of the analysis of this broad component in order to quantify the level of motion-restricted membrane phospholipids in the brains of the individuals being studied.

The failure of our broad component analyses to yield results which harmonize with the rich biochemical literature that is consistent with the membrane phospholipid hypothesis of schizophrenia does insert a possible note of caution, however. It should be noted that, given the low signal-to-noise in 31-phosphorus magnetic resonance spectroscopy, the areas of the peaks obtained are inherently variable (Puri et al., 2008a). This is particularly true of the underlying broad component, which has a coefficient of variation double that of the other peaks visible in the spectrum (Hamilton et al., 2003b). One should take into account the possibility that this variability may be masking any changes in the broad component, leading to a reduction in the ability to monitor membrane phospholipids.

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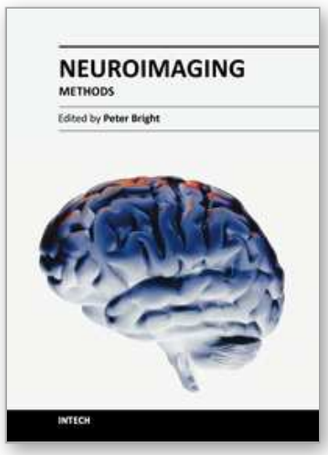

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Neuroimaging methodologies continue to develop at a remarkable rate, providing ever more sophisticated techniques for investigating brain structure and function. The scope of this book is not to provide a comprehensive overview of methods and applications but to provide a 'snapshot' of current approaches using well established and newly emerging techniques. Taken together, these chapters provide a broad sense of how the limits of what is achievable with neuroimaging methods are being stretched.

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