Human brain mapping under increasing cognitive complexity using regional cerebral blood flow measurements and positron emission tomography

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AIM

The aim of this thesis was to implement and evaluate methods to perform human brain mapping studies of behaviours of increasing cognitive complexities using positron emission tomography (PET) and regional cerebral blood flow (rCBF) measures, and to understand the underlying limitations and advantages of existing methods revealed through the introduction of a new PET rCBF tracer, Carbon-10-labelled carbon dioxide ($^{10}CO_2$), and a new two-tissue compartment kinetic model for the quantification of rCBF using oxygen-15 labelled water ($H_2{}^{15}O$).

INTRODUCTION

The process of assigning a physiological parameter signifying some aspect of brain function to a spatial representation of the brain defines the term "functional neuroimaging". The overall medically relevant aim is to attach physiological validity to brain-behaviour models at the systems level, and provide a space where physiological predictions and hypothesis can be made in conversation with these models furthering the understanding of the intact and diseased brain. The neuroimaging techniques, primarily PET and functional magnetic resonance imaging (fMRI), enable documentation with very accurate spatial localization of the neurobiological organization in the human brain of often very complex behavioural manifestations and their dynamic interactions in vivo. The physiological basis for functional neuroimaging using PET is the coupling between regional cerebral glucose metabolism (rCMRglc), rCBF and regional neural activity (Villringer and Dirnagl 1995). The exact mechanisms are still debated and a thorough discussion lies outside the scope of this thesis.

From its onset the study and use of rCBF had a particular geographical affinity to Copenhagen and the southern Swedish towns of Malmø and Lund. It was here that professors Niels A. Lassen and David Ingvar in the 1960'ies established methods that quantified rCBF using intracarotid injections of Xenon-133 (Høedt-Rasmussen 1967) and directly demonstrated in normal man its modulation with mental activity (Ingvar and Risberg 1965; Lassen et al. 1978; Roland and Larsen 1976; Roland et al. 1977). They were for at least a decade almost alone among neuroscientist worldwide in embracing this principle (Raichle 2000). Functional brain mapping using rCMRglc PET was applied early on (Mazziotta et al. 1981a), however only initially, as speed of data acquisition and repeatability is important determinants (Raichle 2000). Thus, shorter-lived rCBF PET tracers such as oxygen-15 labelled water ($H_2{}^{15}O$) are preferable.

METHODOLOGY: rCBF MEASURED BY PET

^{15}O-LABELLED WATER AS A rCBF PET TRACER

Accurately quantifiable rCBF measures using both tomographic and non-tomographic techniques have had great importance in the understanding of the pathophysiology of the brain, e.g. in cerebrovascular disease, particularly acute ischemic stroke. Thus, much interest has been directed at characterizing the "penumbra", a zone of non-functioning, but viable, neural tissue with a rCBF of around 0.20 ml•min^{-1}•g^{-1} surrounding the irreversibly damaged ischemic core (Astrup et al. 1981; Baron 1999; Lassen 1990; Trojaborg and Boysen 1973). The penumbra may progress to infarct in hours to days, but is potentially salvageable if reperfused, e.g. by thrombolytic therapy, within this time window with important implications for long-term clinical outcome.

The most widely applied rCBF PET tracer both for quantification and in activation studies is $H_2{}^{15}O$. This is because of the short half-life (123 sec) that allows sequential studies, the ease of production and administration, and low toxicity. The first published paper with $H_2{}^{15}O$ as a quantitative rCBF PET tracer was in 1969, where Ter-Pogossian and co-workers employed intracarotid injections of the tracer mixed with blood using washout kinetics (Ter-Pogossian et al. 1969). Presently, quantification is most likely to be based on an adaptation of the Kety tissue autoradiographic method (ARG) (Kety 1951; Kety 1960). A freely diffusible, biologically inert radiotracer is injected intravenously, followed by a measurable progressive accumulation of regional counts in the brain. However, $H_2{}^{15}O$ is not a fully ideal rCBF tracer, primarily due to it's limited diffusion across the blood-brain-barrier (Bolwig and Lassen 1975; Eichling et al. 1974). The water extraction has been measured to be between 87% (Friis et al. 1980) and 94% (Paulson et al. 1977). As ARG assumes diffusion equilibrium between tissue and venous blood, rCBF will be progressively underestimated at high rCBF values (Herscovitch et al. 1983; Herscovitch et al. 1987; Pawlik et al. 1993; Raichle et al. 1983). Better flow tracer characteristics can be obtained with the lipophilic ^{15}O-labelled n-butanol. However, this tracer is metabolized and, thus, not biochemically inert. Moreover, it has a more complicated radiochemical synthesis that could limit total number of scans feasible, and there are uncertainties about the exact brain blood partition coefficient in humans (Pawlik et al. 1993). Although, the quantitative differences between the two tracers are in the order of 5-10 ml•min^{-1}•g^{-1} in grey matter, direct comparisons have not shown appreciable performance differences in human brain mapping studies (Quarles et al. 1993).

TRACER KINETICS – THE AUTORADIOGRAPHIC ONE-TISSUE COMPARTMENT MODEL USING $H_2{}^{15}O$

In the ARG the regional counts are summated over a given time period and represented by a single static PET scan, *R*. This scan can be converted to represent the distribution of regional tissue concentrations via scanner cross calibration. The model explains R by the rCBF, often denoted as *f*, and the radioactivity concentration of the arterial input function over time, $C_a(t')$. The final formulation of the one-tissue compartment model gives:

$$R = \int_{t_1}^{t_2} R(t)\,dt = f \int_{t_1}^{t_2} \int_{0}^{t} C_a(t')\exp\left[-(f/p)(t-t')\right] dt'\,dt \qquad \text{eq. (1)}$$

where $R(t)$ refers to instantaneous tissue concentration at time t, and R to the accumulation integral from scan start, t_1, to scan end, t_2. The averaged brain tissue-to-blood partition coefficient of water, p, is fixed. A look-up table can be calculated for conversion of local tissue counts, R, and the corresponding f or rCBF (Alpert et al. 1984; Kanno et al. 1987; Kanno and Lassen 1979; Reivich et al. 1969). It is essential that the arterial input function is corrected for delay and

deconvolved with the dispersion function (Iida et al. 1986). The assumptions are that *p* and rCBF are homogenous in a region of interest, and that rCBF is constant within the period of measurement.

LIMITATIONS OF THE AUTORADIOGRAPHIC ONE-TISSUE COMPARTMENT MODEL

Already in the initial implementation of the model it was recognized that there would be a problem with tissue inhomogeneity (Herscovitch et al. 1983), which simply adheres to the inability to correctly quantify the regional radioactivity distribution using methods of limited spatial resolution, such as PET (Hoffman et al. 1979; Mazziotta et al. 1981b). As PET scanner resolution is finite, the counts in a region of interest (ROI) is likely to represent a volume-weighted average of contributions from different tissue segments, e.g. grey matter, white matter, oedematous, and neoplastic tissues, each with different rCBF's and partition coefficients. Some of these counts arise from crosstalk from neighbouring regions with "spill-out" of counts from high activity structures, usually grey matter, and "spill-in" to low activity structures, usually white matter and cerebral spinal fluid (CSF). This phenomenon is termed the partial volume effect (PVE) (Figure 1). In other words there is a confounding influence of the size of a structure on the values quantified. This can be particularly disturbing in patients where cerebral atrophy can be present (Regeur et al. 1994), because loss of tissue volume can appear as loss of function with the risk of diagnostic misinterpretations (Herholz et al. 2002). The clinical PET image reading should, thus, ideally be performed with reference to structural MRI (Chao et al. 2001).

In healthy subjects the PVE will lead to a systematic underestimation of what is assumed to be grey matter ARG PET rCBF with values found in the 0.40-0.55 ml•min^{-1}•g^{-1} range (Hatazawa et al. 1995; Iida et al. 1998; Kanno et al. 1987; Matthew et al. 1993; Treyer et al. 2003). These values were about half those found for the fast, putatively grey, flow component using the xenon clearance technique in the 0.80-0.90 ml•min^{-1}•g^{-1} range (Høedt-Rasmussen 1967). Moreover a dependency of the rCBF values on the total data accumulation time was identified (Raichle et al. 1983).

TRACER KINETICS – THE DYNAMIC TWO-TISSUE COMPARTMENT MODEL USING $H_2{}^{15}O$

In response to the above considerations, correction strategies of the arterial input function were developed (Iida et al. 1986), and a more accurate parallel two-tissue compartment model was proposed (Gambhir et al. 1987). The concept of the perfusable tissue fraction, α, that denotes the net fractional mass of tissue in a ROI that is capable of exchanging water, was intended to exclude non-perfused spaces, such as CSF, and to address the systematic rCBF underestimation in the autoradiographic method introduced by the PVE (Iida et al. 1989) (Figure 1). The perfusable tissue fraction was integrated into early models based on intra-arterial injections of Xenon-133 (Høedt-Rasmussen 1967) or $H_2{}^{15}O$ (Ter-Pogossian et al. 1969), external stationary sodium iodide detectors and a two-tissue compartment clearance model that, however, being non-tomographic did not allow estimation of absolute functional volumes.

In our implementation using $H_2{}^{15}O$ and PET (eq. 2) we validated four different models, two one-tissue compartment models with and without a vascular term and two two-tissue compartment models with a white matter, or more correctly "slow" component, flow that was either fixed at 0.20 ml•min^{-1}•g^{-1} or variable. The aim was to segregate, based on kinetic behavior, the tissue compartments in a ROI, and assign a perfusion value and a functional volume to each compartment (Figure 2). The models were applied to the macaque monkey (IV) and human (V). Our approach followed traditional procedures within the field identifying the optimal model using the Akaike Information Criteria (Akaike 1974), performing error sensitivity analysis, describing parameter sensitivity towards length of fit, data acquisition mode (2D vs. 3D), and the effects of regional perturbations of rCBF by visual stimulation. Further reproducibility measures were performed dependent on ROI size and in the monkey study the resulting absolute functional tissue volumes were compared with stereologically obtained measures from the same regions.

The optimal model in both monkey and man (IV, V), was the two-tissue compartment model with a fixed value for the "slow" component flow with the following formulation

$$R(t) = \alpha_g \bullet f_g \bullet C_a(t) \otimes e^{-\frac{f_g}{p_g}t} + \alpha_w \bullet f_w \bullet C_a(t) \otimes e^{-\frac{f_w}{p_w}t} \qquad \text{eq. (2)}$$

where f_g is the fitted "fast" component rCBF value [ml•min^{-1}•g^{-1}], while f_w is fixed at 0.20 ml•min^{-1}•g^{-1}, and α_g and α_w are the perfusable tissue fractions [g ml^{-1}] for the "fast" and "slow" components, respectively. The convolution operator is denoted by $\otimes$, and the averaged brain tissue-to-blood partition coefficient of water for grey and white matter, p_g and p_w, are fixed at 1.0 ml•g^{-1} and 0.8 ml•g^{-1}, respectively (Herscovitch and Raichle 1985). It should be noted that the (apparent) volume distribution of water, V_d, is equal to αp. With this model we found an optimal length of fit of 6 min, which was the longest interval tested. The reproducibility of the "fast" flow component was approximately 15% in a 1200 voxel (21.6 ml) ROI, where approximately $^1/_3$ of the ROI was grey matter on an ARG image, and, because of the increased noise level, worse with smaller ROI's (V).

With conventional ARG, values in putative grey matter were in the expected range (0.4 ml•min^{-1}•g^{-1}), while the estimated values in the "fast" component CBF were doubled in the monkey study (0.8 ml•min^{-1}•g^{-1}), and increased 2.5 times in the human study (1.1 ml•min^{-1}•g^{-1}) using the optimal model (IV, V). These values are closer to or higher than those obtained by standard Xe-133 clearance models (Høedt-Rasmussen 1967). The lower estimated values in monkey compared to the human study could be explained by the ketamine/xylazine anesthesia used during the measurements in the latter. While ketamine alone can increase CBF (Hougaard et al. 1974) the combination with xylazine may actually give a decrease (Lei et al. 2001). Although the "fast" component CBF in the monkey study (IV) could have been underestimated, our data nevertheless clearly demonstrates the deteriorating effect of the PVE.

As $H_2{}^{15}O$ is diffusible to a limited degree, activity will be present particularly in the arterial intravascular compartment, V_a [ml•ml^{-1}], which cannot be separated from tissue activity using a one-tissue

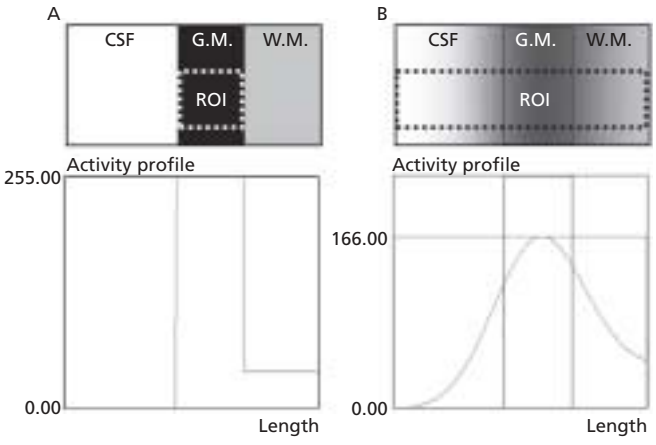

Figure 1. An illustration of the partial volume effect. Under ideal conditions (A) a region of interest (ROI) can be drawn that only sample counts from the grey matter (G.M) compartment, but in a PET scanner (B) the limited resolution will "blur" the image and the result is a net "spill-out" of counts from the grey matter compartment and a "spill-in" to the white matter (W.M.) and CSF compartments. The ROI's in autoradiography and one-tissue-compartment kinetic modeling are often defined as in (A) to sample the grey matter activity, but this does not represent the true compartment activity as can be seen from the activity profiles in (B). As the underlying structure often is unknown the parameter estimation strategy in papers IV and V is to place ROI's sufficiently broad to capture spill-over counts (B), followed by estimation of the perfused fractions of grey and white matter, and indirectly the CSF space.

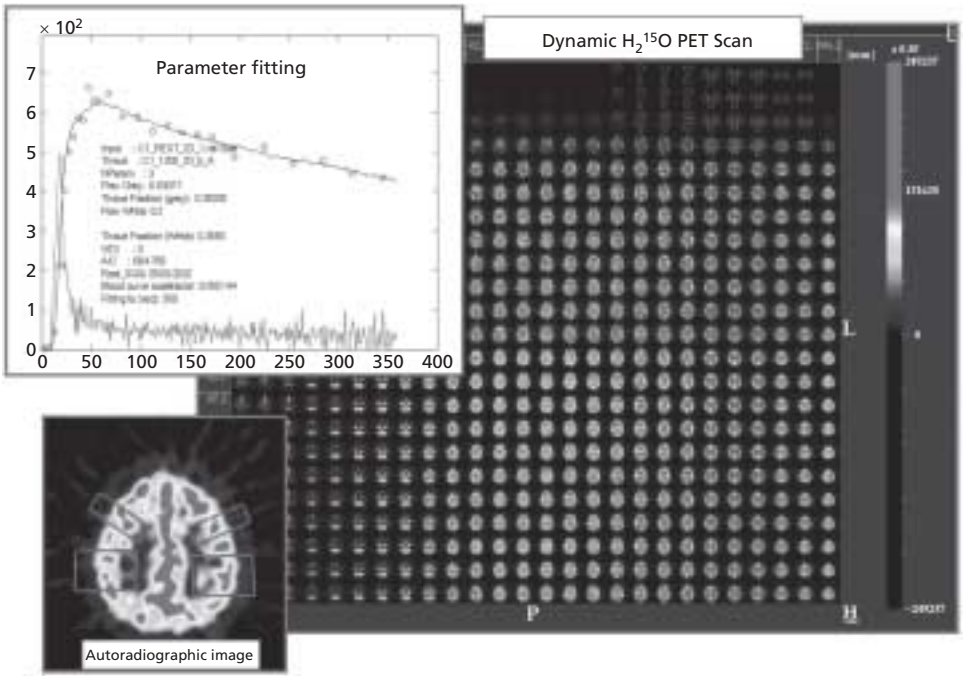

Figure 2. The ROI's, defined with reference to an autoradiographic image, are transferred to the dynamic data extracting the dead-time corrected time-activity curve (R(t) which are fitted over 6 minutes (left upper insert). The lower curve is the down-scaled delay and dispersion corrected arterial input function, Ca(t).

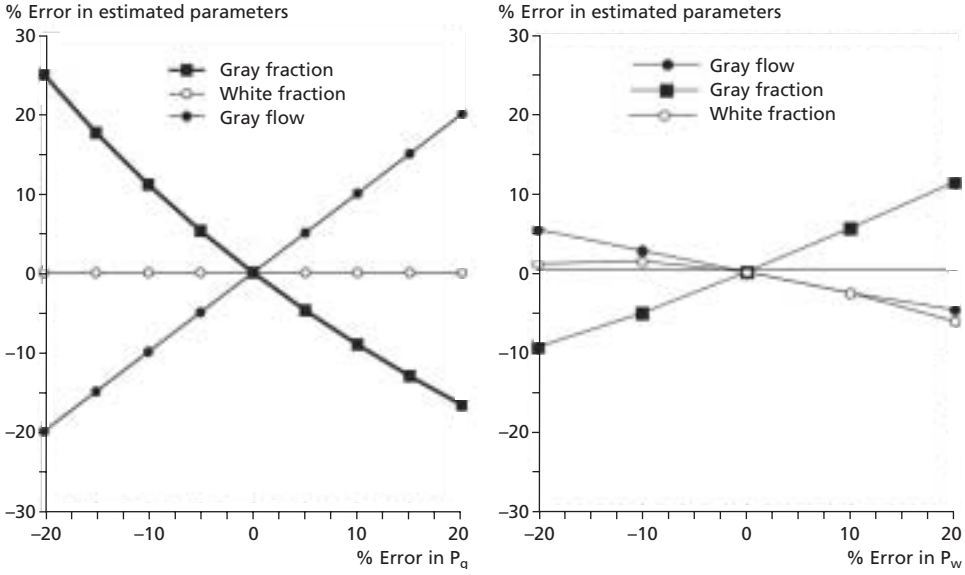

Figure 3. Results from a simulation study demonstrating the effects of errors in the fixed values of the partition coefficients of grey matter (p_g, left) and white matter (p_w, right) on the estimated parameters using the model in eq. 2 with a fixed white matter flow, f_w, of 0.20 ml•min^{-1}•g-1. See (IV) for details on the simulation procedure.

compartment method. The significance of correcting for this parameter, and even using it as independent physiological information, has been stressed (Fujita et al. 1997; Ohta et al. 1996). We have not been able to find significant improvements in the quality of our one-tissue compartment models introducing this parameter (IV, V) even when comparing the models at a fit period of 3 min as in the original implementation. This could, however, be a function of the ROI's selected, as further support of the inclusion of V_a has been presented in a recent paper (Ito et al. 2001). As we are using a very long fitting period this parameter is not expected to influence our fitted rCBF parameters significantly (Ohta et al. 1996).

THE PARTITION COEFFICIENTS AND PERFUSABLE TISSUE FRACTIONS

As opposed to steady-state or ARG single-scan techniques (eq. 1) it is customary in one-tissue compartment kinetic rCBF modelling to fit, rather than fix, the (apparent) regional volume distribution of water, $V_d = \alpha p$ (Huang et al. 1983; Iida et al. 1989; Ito et al. 2005; Koeppe et al. 1985; Ohta et al. 1996). It is assumed that a ROI is filled with a single homogeneously perfused tissue, thus α = 1.0 g•ml^{-1} and $V_d = p$. However, this assumption can usually not be fulfilled for cortical grey matter because of the PVE. The cortical thickness is small (2-3 mm) (Oster et al. 1993; Regeur et al. 1994) relative to the effective PET scanner resolution using $H_2{}^{15}O$ (8-10 mm). Thus, the inclusion of non-perfused space and variations in the mixture of grey and white matter in the ROI will lead to an underestimation of the fitted V_d value in cortical grey matter relative to the true partition coefficient (Iida et al. 1989). The intention of our model formulation (eq. 2) was to correct for these effects using fixed brain tissue-to-blood equilibrium partition coefficient values of water for grey and white matter, p_g and p_w, based on in vitro values from the literature (Herscovitch and Raichle 1985). Deviations from these values can occur as a function of neurodevelopment status (Volpe et al. 1985) or under pathological conditions e.g. cerebral oedema, where the white matter partition coefficient can increase from 0.83•ml g^{-1} approaching grey matter values, 0.96•ml g^{-1} (Herscovitch and Raichle 1985). This will lead to model dependent errors in the calculated values for tissue flow and PTF. For p_g the sizes of these errors can easily be derived. From eq. 2 it follows that the *ratio* of f_g/p_g is a constant, thus 10% error in p_g will propagate linearly to a 10% error of f_g. Likewise the *product* of $p_g\alpha_g$ is a constant, thus a 10% error in p_g translates non-linearly to a – 9% error in α_g. The effects of errors in p_w can be simulated (Figure 3).

We were able to find significant correlation between a fitted frac-

tion, α_g, that can be converted to an absolute functional volume of the "fast" component, with an independent stereological measure of grey matter tissue volume (IV). This supports the contention that the perfusable tissue fractions reflect the regional tissue composition. The absolute value, however, was approximately 40% lower. To explain this difference by an erroneously assumed grey matter partition coefficient alone, the true value would have to be 0.60 ml•g^{-1}, which is not sustainable. The sensitivity to other potential error sources in eq. (2) was not a likely explanation of this discrepancy either (IV). It can be speculated that there are violations of the assumptions of a parallel compartmental organization with direct diffusion of $H_2{}^{15}O$ from the "fast" to the "slow" compartment. Alternatively or supplementary more than two significant compartments could exist including a grey matter subcompartment with particularly fast $H_2{}^{15}O$ washout. A similar finding has been reported previously comparing intracarotid injections of Xenon-133 in saline and blood labelled with $H_2{}^{15}O$ using the clearance method. Although the global CBF values did not differ appreciably, the "fast" component perfusable tissue fraction using $H_2{}^{15}O$ was about half that of using Xenon-133 (Ter-Pogossian et al. 1971), and reported "fast" component flow values were in the 1.0 to 1.6 ml•min^{-1}•g^{-1} range (Ter-Pogossian et al. 1969), thus, similar results to our study. It was hypothesized that this difference arose from the ratio of white to grey matter partition coefficients, 1.88 and 0.8, for Xenon-133 and $H_2{}^{15}O$, respectively. The lipophilic nature of the former could tend to segregate grey and white matter based on anatomy, while the only slight difference in water content between grey and white matter would depress anatomical differences and separate on functional criteria when using $H_2{}^{15}O$. There can, however, be a sampling bias in this study, as the attenuation coefficient in tissue of the 81 keV γ ray emitted by Xenon-133 is about twice that of the resulting 511 keV from $H_2{}^{15}O$, effectively reducing the relative contribution of the deeper seated structures in the former. The effects of this would depend on the white/grey matter composition of these structures, which is not clearly documented.

In our implementation it was verified that the size of the "fast" flow compartment did not change significantly with the increase in rCBF during visual stimulation as would be predicted if this compartment related to anatomical structures or a stable and defined functional compartment. The size of this "fast" flow fraction has been found reduced in patients with cerebral pathology (Høedt-Rasmussen and Skinhoj 1966). Thus, with a full 3D tomographic technique such as PET, fractions could easily be converted into absolute functional volumes that together with the PVE corrected rCBF value could prove to be a relevant parameter in neurodegenerative disease.

A NOVEL rCBF PET TRACER: CARBON-10-LABELLED CARBON DIOXIDE

Carbon-10-labelled carbon dioxide ($^{10}CO_2$) has unique qualities as an inhaled rCBF PET tracer, and was developed in cooperation between the physicists at the PET and cyclotron unit at Rigshospitalet and The Department of Medical Physics at the University of Wisconsin (Alves et al. 2000; Holm et al. 1999; Jensen et al. 1998; Nickles et al. 1998). The half-life of $^{10}CO_2$ is only 19.3 seconds, which enables multiple independent measures at short interval. Without increasing the total effective dose (ED) to the subject above 6.0 mSv the number of independent scans can be increased from 12-14 with $H_2{}^{15}O$ to 64 with $^{10}CO_2$. The ED at steady state inhalation has been calculated to 0.60 μSv•MBq^{-1}•min^{-1} (Holm et al. 1999). It should be noted, however, that the "information" in terms of the total sum of effective brain counts per total effective subject dose sampled in a $^{10}CO_2$ session is not different from an average $H_2{}^{15}O$ session. Thus, what $^{10}CO_2$ offers is the option of dose fractionation. This will increase the number of different conditions that can be explored with retained or improved statistical power of the analysis, that can diminish the effects of random biological variation and, despite the increase in Poisson noise, better the estimates of the true mean value of regional activity in a given condition (VI). This can be done without prolonging the total time in the scanner for the subjects compared with $H_2{}^{15}O$, which could otherwise compromise this benefit by increasing the possibility of head movement artefacts.

Carbon-10-labelled carbon dioxide has only been used in human brain mapping in one published study so far (VI). Herein we validated the tracer indirectly by applying the well-characterized annular reversing checkerboard paradigm with parametrically varied stimulus reversal frequencies (Fox and Raichle 1985). By the use of a set of polynomial expansions (Taylor series) of the stimulus reversal frequency (Buchel et al. 1996) the locations with significant 2'nd or 3'rd order dependencies in the visual cortex and the frequencies by which they showed maximal response (10-15 Hz) could be identified on a single subject level. This is in essence the strength of this isotope separating it from rCBF PET using $H_2{}^{15}O$ and fMRI; the ability to gather multiple repeated whole brain volume measures of the rCBF distribution in a single subject.

The kinetic model for $^{10}CO_2$ rCBF quantification is in theory simple using a steady state principle, but the regional values will be influenced by the distribution of tracer appearance times in the brain. For $H_2{}^{15}O$ there is a difference of approximately 4 seconds of tracer appearance between the lentiform nucleus and the cerebellum (Iida et al. 1988; Iida et al. 1989). Assuming that this range is similar for $^{10}CO_2$, this translates to a signal loss, by the differences in half-life alone, of 11% between these two locations, or 6% from the whole brain average. This does not impair the application of the tracer in brain mapping studies as these are based on subtraction logic. Thus, the regional signal loss will affect the resting and active conditions alike with a negligible increase in Poisson noise contribution. The challenges in the day-to-day practical use have primarily been in establishing a stable $^{10}CO_2$ activity output over a scanning session. Hence, a larger scale routine use would demand cyclotron target developments.

INSTRUMENTATION EFFECTS ON rCBF QUANTIFICATION – 2D VS. 3D DATA ACQUISITION

A dramatic increase in sensitivity of the PET instrumentation was introduced to the field with the implementation of 3D data acquisition techniques (Cherry et al. 1991; Townsend et al. 1989). This is obtained by the retraction of the tungsten septae from the field-of-view, which increases the number of active lines of response, thus increasing sensitivity. Unfortunately not only sensitivity, but also the scatter fraction is affected, which increases to an average of 34% compared to 10% in the 2D acquisition mode with septae inserted (DeGrado et al. 1994). The cylindrical scanner geometry of the Advance-GE PET camera results in a nonuniform triangular shaped sensitivity profile along the scanner axis being up to a factor 7 larger during 3D acquisition in the centre slice and lowest, and even lower than with 2D acquisition, at the peripheral slices (DeGrado et al. 1994; Lewellen et al. 1996). This can be an issue with respect to brain studies on older 15 slice PET systems with axial field of views of approximately 9 cm, as this is effectively reduced to 7 cm (Cherry et al. 1991), but with the 15 cm field of view in the Advance-GE PET camera the sensitivity benefit of 3D acquisition can be applied on a full brain volume if placed correctly in the scanner opening. The benefit is a dramatic decrease in injected dose or scan length with unaltered image counts, or conversely an increase in the number of scans performed within a given dose maximum, and, thus, the statistical power of an experiment. If low count rate in 2D is an issue, the increased 3D sensitivity can also increase resolution by allowing sharper reconstruction filters (Trebossen et al. 1998), permitting the identification of smaller and more discrete changes. The limitations using 3D is the increase in data acquired, which may in some cases influence a protocol using dynamic sampling (V).

A number of studies have evaluated the consequences for the quantitative parameters using 3D vs. 2D acquisition with matched

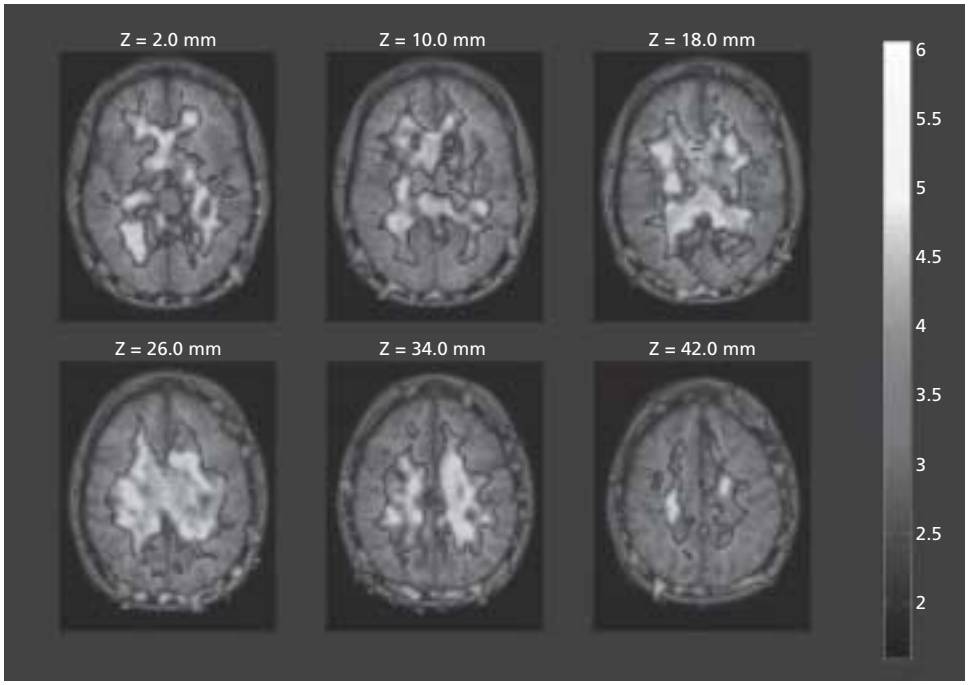

Figure 4. Statistical parametric map of Z-scores projected onto their average magnetic resonance imaging (MRI) scan showing the main effect of 3D vs. 2D data acquisition. Eight healthy volunteer have contributed 4 scans during each acquisition mode and significant changes are found only in white matter and some extra-cerebral areas. Images are thresholded at $p < 0.001$ ($Z > 3.09$). Data derived from (V).

counting statistic. In general, scatter correction is necessary for accurate quantification in both dynamic and static imagery (Dhawan et al. 1998; Stearns 1995; Trebossen et al. 1998), and there is a systematic overestimation of radioactivity concentration in areas of low activity. This will influence the obtained values in methodology based on static imaging, e.g. in ARG.

Thus, in quantification of the rCMRglc the correspondence between grey matter values in the two acquisition modes were excellent. However, the 3D white matter values were overestimated by approximately 20% (Dhawan et al. 1998). This corresponds to our own findings of a systematic and significant increase in white matter rCBF using ARG from 0.17 $ml \cdot min^{-1} \cdot g^{-1}$ to 0.21 $ml \cdot min^{-1} \cdot g^{-1}$, for 2D and 3D acquisition respectively, while grey matter rCBF was not influenced (V) (Figure 4). The contributing factors for this effect are inadequately corrected scatter from out of the field activity and neighbouring high activity areas, the decrease in axial spatial resolution during 3D, and the use of 2D transmission scans in the reconstruction of 3D data. Large area activation, as seen in the visual cortex during checkerboard stimulation, was not significantly different (behavioural state vs. acquisition mode interaction effect) during 2D and 3D acquisition neither in peak areas nor in the periphery (V). This indicates that any inadequately corrected contributions of scatter is identical during control and stimulation and will cancel out on subtraction (Cherry et al. 1993). Thus, the primary importance of this difference would be in the evaluation of low rCBF regions such as the ischemic penumbra (Astrup et al. 1981), or in the comparisons between techniques. There were no significant differences in the parameters using a dynamic kinetic model (V).

The improved sensitivity in 3D acquisition and $H_2{}^{15}O$ rCBF studies do not apply to doses above 800 MBq on the Advance-GE PET scanner. There will be an increase in random events leading to a net reduction in useful counts, the noise equivalent counts (NEC's), above this level (Figure 5) (Holm et al. 1996). Activation studies in 2D acquisition solely for brain mapping purposes, as performed previously (I; II; Blinkenberg et al. 1996), are no longer used under regular conditions. With an injected activity of 1000 MBq $H_2{}^{15}O$, an ED of 0.93 $\mu Sv \cdot Mbq^{-1}$ (ICRP 1998), and a dose limitation in Denmark of approximately 6.0 mSv per healthy subject, the total number of PET scans in 2D will be limited to six. Conversely, using 3D acquisition we now use a dose of 400 MBq in a PET session of 12 repetitive injections or 200 MBq for 24 injections divided on two sessions (III; V; Balslev et al. 2002; Born et al. 2002; Bundesen et al. 2002; Gerlach et al. 2002a; Gerlach et al. 1999; Gerlach et al. 2000; Gerlach et al. 2002b; Gerlach et al. 2002c; Gerlach et al. 2004; Holm et al. 1996; Hugdahl et al. 1999; Hugdahl et al. 2000; Humphreys et al. 2004; Jernigan et al. 1998; Kjaer et al. 2002; Larsen et al. 2000; Larsen et al. 2005; Lou et al. 1999; Nour et al. 2000; Nowak et al. 1999; Poline et al. 1996; Scheuer et al. 2005) Thus, the benefit of moving to 3D is obvious. When performing *quantitative* rCBF studies in 3D the maximal number of studies may be less owing to the increased time spent with the practical maintenance of arterial blood sampling (Law et al. 2002; Rostrup et al. 2005; Rostrup et al. 2000; Rostrup et al. 2002).

THE OPTIMAL SCAN LENGTH

Although rCBF is rarely quantified in PET brain mapping studies, the shape of the input function to the brain (determined, among other things, by the tracer injection protocol) and the rCBF values of the tissue of primary interest are instrumental in optimization of the S/N to a particular behavioural manipulation. The principle is fast exchange in high flow components and slow exchange in low flow components. In the initial adaptation of the ARG technique a scan duration of 40 sec was used after bolus $H_2{}^{15}O$ injection (Herscovitch

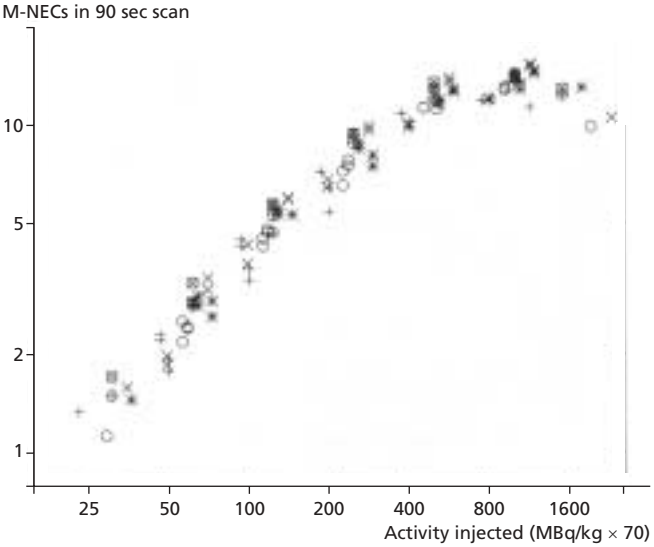

Figure 5. Noise equivalent counts × 10^6 (M-NEC) in a 90 sec scan as a function of injected $H_2{}^{15}O$ dose using the Advance-GE scanner. A gradually reduced utilization efficiency is seen up to a dose of 800 MBq. N = 8. From (Holm et al. 1996).

et al. 1983; Raichle et al. 1983). This roughly corresponded to the brain tissue delivery phase and meant that the regional tracer distribution was proportional to regional flow according to the bolus fractionation principle. These early images can be noisy as isotope decay is stochastic and show Poisson distributed variance. Thus, there is an advantage in prolonging the integration periods and increasing sampled counts. Unfortunately, when using a freely diffusible tracer, such as $H_2{}^{15}O$, the distribution between grey and white matter counts change dynamically decreasing contrast. Hence, over time S/N will primarily increase in the lower perfused white matter that is rarely the tissue of interest, while the grey matter will not improve as much. Progressively increasing scan durations have been compared directly, and an optimum has been found at a scan interval of 90 sec commencing after bolus injection (Kanno et al. 1991). Further, this longer scan time improves robustness of determined rCBF values against misestimations of the delay and dispersion of the arterial input function (Iida et al. 1986; Kanno et al. 1987).

The known dynamic changes of $H_2{}^{15}O$ in the brain described above have been exploited to maximize the regional difference signal in human brain mapping experiments. The strategy is to switch off the activation condition at the earliest when the $H_2{}^{15}O$ bolus tissue uptake is complete around 30-40 sec after arrival to the brain. This reduces rCBF in activated areas and, thus, tracer washout and signal loss favouring prolongation of the scan length. The gain in S/N can be estimated to about 10%, when a switch is only applied to the active task (single switch protocol) (Cherry et al. 1995). It is predominantly behaviourally induced rCBF events that occur during the uptake phase, and particularly the centre 15 sec that determines the final activity distribution image (Iida et al. 1991; Silbersweig et al. 1994). This strategy cannot be used in quantitative studies that assume physiological steady state. Using a regional group statistical test as a cost function marginally larger Z-values using 60 sec acquisition protocols have been found (Johannsen et al. 1998; Sadato et al. 1997), but these were performed during behavioural activity throughout the session without switch, which would tend to decreased regional integrated values due to tracer wash-out (Silbersweig et al. 1993). In recent non-quantitative PET activation studies from various institutions based on a single time frame scan, lengths covering the range from 60 sec (Herbster et al. 1997; Rumsey et al. 1997), 80 sec (Petit et al. 1999), 90 sec (Dang-Vu et al. 2005; Fink et al. 1996; Grafton et al. 2001; Mellet et al. 2000), and 100 sec (de Jong et al. 2001) can be found. These differences are not likely to give appreciable difference in the results obtained. We have selected a 90 sec acquisition protocol based on the above considerations (Cherry et al. 1995; Kanno et al. 1991; Silbersweig et al. 1993).

OTHER METHODOLOGICAL ASPECTS

There are several additional methodological challenges to the use of PET for human brain mapping, including imaging issues such as: the physical basis of positron emission and annihilation, image reconstruction and filtering, attenuation correction, image resolution; and very importantly, image analysis issues, such as: image alignment, co-registration with MRI, stereotactic normalization, Gaussian filtering and statistical modelling, data presentation and rendering. For human brain mapping using PET there is now broad consensus about the optimal parameters, with analyses following a number of established paths. Discussion of these aspects has been dealt with in several books (Thatcher et al. 1994; Toga and Mazziotta 1996) and is publicly available (http://www.fil.ion.ucl.ac.uk/spm/doc/books/hbf2).

APPLICATION OF THE TECHNIQUE

BRAIN MAPPING OF READING IN THE JAPANESE LANGUAGE

The initiation of the "lesion paradigm" of indirect functional localization of behaviour in the brain took it's beginning from the investigation of the faculty of language (Broca 1861), and, in terms of the generation of large scale interest, so did the application of cognitive neuroscience to functional brain imaging (Petersen et al. 1988; Petersen et al. 1989). The unique possibilities of functional brain imaging in this particular domain originate from the lack of animal models. The study of language can only be carried out in human subjects. The difficulties related to the "lesion-paradigm" adhere to the lack of anatomical precision. Cerebral lesions are after all accidental, and will often be dependent on factors such as vascular territories. Further, problems arise from the multifaceted cognitive psychological profiles in patients employing compensatory strategies, both cognitively and neuronally, and the possible contribution of remote effects or disconnections of undamaged areas. Thus, from a lesion deficit study it can only be concluded that the neuronal structures in or connections passing through the lesioned areas were necessary for the lost function. The neuroimaging studies, although not without pit-falls, can display the whole sufficient neural network participating in the intact brain and constitute an important supplementary strategy of investigation. However, an activated area explains very little in itself, and to interpret the possible task components involved, lesion data are an important source of evidence (Price 2000). Recently, this strategy has been improved using transcranial magnetic stimulation (TMS) to temporarily induce a reversible "lesion deficit" in the neural information processing to interactively confirm the necessity of a region identified by functional imaging (Balslev et al. 2004; Devlin et al. 2003).

The orthography of a language is the set of rules of how to write correctly in the writing system of a language. Phonology refers to word sound, and semantics to word meaning (Table 1). In the Japanese language there are two dominant orthographic systems, Kana consisting of 71 characters and Kanji with more than 40.000 characters listed in dictionaries of which 2.000 is recommended for standard use. Kana characters are all syllabograms (phonograms) from which all Japanese words can be constructed. The phonetic value of Kana is fixed regardless of the relative position in a word. The Kanji characters, on the other hand, are morphograms (ideograms, pictures), based on Chinese characters, and give semantics and phonology simultaneously. Kanji characters can only be written if learned and memorized (Soma et al. 1989), and mostly contain an established phonetic value determining the exact pronunciation. Thus, Kana words are comparable to regular words in the Indo-European language with an almost complete grapheme-to-phoneme correspondence (shallow orthography), while Kanji words would be equivalent to irregular words employing a lexical reading system based on the generation of a whole-word image (deep orthography).

Table 1. Definitions of linguistic and neuropsychological terms.

Term	Definition
Agraphia	An acquired loss of the ability to write caused by a disorder of the CNS
Alexia	An acquired loss of the ability to read caused by a disorder of the CNS
Anomia	An acquired loss of the ability to name objects caused by a disorder of the CNS
Dyslexia	A disorder marked by a severe difficulty in recognizing and understanding written language, leading to spelling and writing problems
Grapheme	Any of a set of written symbols, letters, or combinations of letters that represent a phoneme
Morphogram	A symbol that directly, but abstractly, represents the thing or concept itself rather than the word for it
Orthography	The set of rules of how to write correctly in the writing system of a language.
Phoneme	The smallest phonetic unit of a language
Phonogram	A symbol that represents a word, part of a word, or a phoneme
Phonology	The system or pattern of speech sounds used in a particular language
Semantics	The study of how meaning in language is created by the use and interrelationships of words, phrases, and sentences

Merriam-Webster & Wikipedia online.

Unique to the Japanese language, there exist clinical neuropsychological evidence to suggest that reading of these two systems are organized differently, in that patients with a lesion in the *left angular gyrus* would suffer from alexia with agraphia, the acquired loss of reading and writing ability, respectively, for the Kana writing system, and additionally agraphia for Kanji writing (Iwata 1984; Tanaka et al. 1987), but not alexia for Kanji reading. The alexia also applies to single Kana characters, where no apparent meaning is present. This suggests involvement of the angular gyrus in syllabogram to phonology encoding, rather than word to phonology or semantics. Conversely, a lesion in the *left inferior posterior temporal lobe* would lead to alexia with agraphia for Kanji, but retain the Kana reading and writing abilities, thus, the classical signs of a double dissociation. These intriguing observations have been the focus of a number of clinical neuropsychological (Iwata 1984; Kawahata et al. 1988; Kawamura et al. 1987; Kawamura et al. 1989; Sakurai et al. 1994; Sakurai et al. 2000b; Soma et al. 1989; Sugishita et al. 1992; Tanaka et al. 1987; Yamadori 1975; Yokota et al. 1990), and neuroimaging studies (Callan et al. 2005; Kiyosawa et al. 1995; Lee et al. 2003; Nakamura et al. 2002; Nakamura et al. 2000; Sakurai et al. 2000a; Sakurai et al. 1993; Sakurai et al. 1992; Tokunaga et al. 1999). Neither strategy has revealed completely consistent results, and is, thus, no different from what has been found in the investigation of the Indo-European languages (Grabowski and Damasio 2000; Price 2000).

Kanji single word reading

Evidence from monkey studies have demonstrated a division of the visual pathway into a dorsal route pointing towards the parietal lobes involved in spatial processing (Where is it?) and a ventral route pointing towards the inferior temporal lobes primarily responsible for object recognition (What is it?) (Mishkin et al. 1983). Later human brain mapping studies have confirmed this dichotomy (Haxby et al. 1991) and further explored the neural correlates of object recognition in different categories of objects (Gerlach et al. 2002a; Gerlach et al. 1999; Gerlach et al. 2002b; Martin et al. 1996). The association of the left inferior posterior temporal lobe with the recall of the visual graphical form of Kanji characters, originating from drawings of objects, thus, seems consistent with the overall organization in the visual system. The results from the neuropsychological literature are also fairly consistent in stressing the importance of this region as visual graphical memory storage and in Kanji reading (Iwata 1984; Kawahata et al. 1988; Kawamura et al. 1987; Sakurai et al. 1994; Sakurai et al. 2000b; Soma et al. 1989; Yokota et al. 1990). A lesion in this area can additionally give rise to anomia, again accentuating the association between Kanji reading and object recognition (Sakurai et al. 1994). Converging evidence from functional neuroimaging have shown increased activity in this area when reading Kanji words aloud both compared to Kana (I) and visual fixation (Sakurai et al. 2000a; Sakurai et al. 1992), and similarly during writing actual Kanji word, mental Kanji word writing and mental recall of Kanji words (Nakamura et al. 2002; Nakamura et al. 2000; Tokunaga et al. 1999) that also need access to the graphical memory storage.

Kana single word reading

The function of the angular gyrus in reading is more controversial. Lesions of the left angular gyrus have in classical western neuropsychology been associated with agraphia with alexia (Dejerine 1891; Geschwind 1965) indicating an essential role in grapheme-to-phonology decoding. Thus, this would be in concurrence with the perceived role of this region in the processing of a phonologically based script system, such as Kana. While some lesion studies have supported this model (Iwata 1984; Kawamura et al. 1987; Tanaka et al. 1987; Yamadori 1975), others have not. Some have suggested other locations for the phonological processing, such as the left lateral occipital gyrus (Sakurai et al. 2000b), and some have rejected the proposed dichotomy altogether (Sugishita et al. 1992).

The human brain mapping results have shown similar inconsistencies from the onset. The first direct comparison of Kana and Kanji reading showed an increased activation response in the left angular/supramarginal area (I). Further, the left angular gyrus shows a preferentially increased activity when comparing imagined Kana writing to imagined Kanji writing (Tokunaga et al. 1999), and the left supramarginal gyrus were involved in a phonological task, monitoring the presence of a target vowel in Kana characters (Fujimaki et al. 1999). In the Korean language there is a similar dichotomy between a phonological script system (Han-gul) and one based on Chinese ideographic characters. In a recent fMRI study Japanese subjects were investigated during Kana reading and two levels of training in Han-gul reading of the same 20 single words (Lee et al. 2003). Kana versus Han-gul reading provoked an initial significant increase in the left angular gurus, which, however, disappeared with increased proficiency. Conversely during Han-gul reading the fMRI signal in the left occipital gyrus decreased with training. This was interpreted as the neural correlates of learning to read Han-gul, shifting emphasis from non-linguistic visual patterns recognition to phonological decoding. Thus, when Han-gul reading reaches a proficiency level similar to Kana reading the activation response will equate. A similar activation of the left angular gyrus has been found in Japanese readers after a period of training in reading other non-native phonograms (Thai) (Callan et al. 2005). A number of studies, however, do not show the predicted activity increase during Kana reading compared to visual fixation or Kanji reading (Sakurai et al. 2000a; Sakurai et al. 1993).

Although cross-cultural correlations must be performed with caution, as reading differences have been found e.g. between Italians and English (Paulesu et al. 2000), it can be instructive to observe the more abundant neuroimaging literature from the Indo-European languages. It quickly becomes apparent that the inconsistencies in the functional architecture of phonological processing during reading in the Japanese language are repeated. Left supramarginal or angular gyrus activation during reading is rarely found by comparison to fixation cross, but require comparisons of two active conditions (Jessen et al. 1999), as it was for Kana vs. Kanji reading (I). Besides these, areas in the inferior parietal region (Demonet et al. 1994; Jessen et al. 1999; Paulesu et al. 1993; Petersen et al. 1989; Zatorre et al. 1992), the left superior temporal lobe (Demonet et al. 1992; Paulesu et al. 2000; Pugh et al. 1996; Sergent et al. 1992), and the left inferior frontal lobe (Demonet et al. 1994; Devlin et al. 2003; Paulesu et al. 1993; Paulesu et al. 2000; Pugh et al. 1996; Sergent et al. 1992; Zatorre et al. 1992) have also been involved to varying degree in a number of different language tasks spanning phonetic detection and decision, rhyming judgment, word reading, and passive listening. This diversity has been pointed out (Poeppel 1996) and probably arise from paradigm design decisions, the degree that stimulus segmentation of rimes or phonemes is needed, automatic cascade-like language processing, differing loads on short-term memory (phonological loop), the chosen baseline condition for comparison, sensory presentation modality, stimulus presentation rate, and the nature of stimuli (words, pseudo-words, or letters; number of syllables), true inter-subject cognitive differences in reading strategies, inter-stimulus interval, "difficulty" and the associated emotional reactions (Demonet et al. 1996; Mechelli et al. 2003; Price et al. 1996a). The consensus was that activity in the left supramarginal gyrus, that was present in the majority of the studies, was dependent on phonological load, which was weak e.g. under simple phoneme monitoring tasks or irregular word reading, as Kanji reading might be. This also underlines the importance of reducing the statistical threshold to prevent false negative results for areas to which an a priori hypothesis of activity is connected. In two meta-analyses of single word reading in the Indo-European languages the left angular gyrus did not appear (Fiez and Petersen 1998; Turkeltaub et al. 2002). However, these analyses have had the character of mere "vote-counting" in a quest to identify converging areas of common

activity, while combined individual significance tests from a number of sub-significant studies into one overall pooled test to increase statistical power have not been performed. This has to do with the tradition of only reporting foci above threshold. Thus, this technique is not well suited for *rejection* of the involvement of an area. Contribution to the difficulties in comparisons is that exact replications of a given paradigm are rarely performed, with a few multi-centre exceptions (Poline et al. 1996). Replication studies are not traditionally considered "original" data, although results might deviate. Formal estimation of statistical power in activation studies has been difficult to perform, as this, besides the number of subjects, will depend on a combination of the selection, effectiveness and robustness of all the noise reducing preprocessing steps before statistical analysis, and will be dependent on the anatomical region and the paradigm. So, statistical power is particular to a specific study (Van Horn et al. 1998).

One peculiarity with importance to paradigm design is expressed via the connectionist model of word processing. The recognition of familiar words inhibits competing neural responses to this stimulus within the language system, while non-words will lead to wide retrieval to fit the best semantic and phonological representation (McClelland and Rumelhart 1981). Thus, random meaningless letter strings have been shown to give a paradoxical wider and more reliable activation in traditionally associated language areas in the brain, than real words (Jessen et al. 1999; Price et al. 1996b; Rumsey et al. 1997), likewise when listening to the non-sense of a narrative played backwards (Friberg and Lassen 1991). Perceptual learning might be the general underlining principle, so that unfamiliar, difficult or degraded stimuli increase regional synaptic activity, whether the learning mechanism is improved synaptic transmission for real words (bottom-up processing) or a more effective retrieval strategy (top-down processing) (Schiltz et al. 1999). We have previously seen this for visually degraded words (Jernigan et al. 1998), in the evaluation of difficult objects (Gerlach et al. 1999), and probably also in dichotic listening (Hugdahl et al. 2000).

Clinically, dysfunctional pathways emanating from the left angular gyrus have been associated to developmental dyslexia. Correlation analysis during English reading have shown a strong functional linkage between this area and traditional language areas in control subjects and completely disrupted correlation in dyslexics, demonstrating that dyslexics use other networks, and perhaps a diversity of compensatory developed networks, compared to controls (Horwitz et al. 1998). Further, the activity level in the left angular gyrus was positively correlated to reading skills in control subjects and negatively correlated in dyslexics. Thus, high activity in these patients does not predict high performance, but the opposite, perhaps representing an extreme, but inefficient, reliance of existing intact pathways (Rumsey et al. 1999).

It is likely that all the above listed considerations will also apply for the diversity found when mapping reading in the Japanese language underlining both the complexity of behavior and technique (Grabowski and Damasio 2000; Price 2000).

In conclusion there are sufficient evidence, clinically and from functional neuroimaging, to strongly support the involvement of the left posterior inferior temporal lobe in Kanji reading. The evidences for the involvement of the left supramarginal or angular gyrus are not dismissive, and is found primarily during comparison between two active conditions rather than with fixation cross. Further and larger studies would be required to clarify this.

SACCADIC EYE MOVEMENTS

Detection of movement or visual phenomena of abrupt onset are essential to survival. In a hostile environment moving, novel, unexpected or abruptly presenting objects are most likely to deliver important information of impeding danger or a potential food source. This is associated with rapid moment-to-moment behavioural adaptation, while immobile objects can generally be ignored (Gregory 1958; Yantis and Hillstrom 1994). An early-warning system exists at the very edge of the retina that can only be used to detect movement, but not identify objects. Thus, a stimulus-driven visually orienting "grasp" reflex, a reflex saccade, is initiated rotating the eyes to move the light of the object into central vision, where the fovea, a specialized area of the highest visual resolution, can be mobilized for accurate object identification. The remarkable stability of the saccade generating system spanning the scale from reptiles to man is what emphasizes its evolutionary importance.

A saccade is per definition a movement away from a point of fixation to a new point of fixation. It should be noted that fixation is a relative term, as the eyes move continuously by the so-called microsaccades. These microsaccades counteract neural adaptation that would otherwise lead to complete fading of visual perception. This is one of the paradoxes of our visual system. We need to fixate in order to study the meticulous details of our world, but a perfect fixation would cause it to evaporate (Martinez-Conde et al. 2004). The cerebral organisation of the human system for foveal fixation, saccades and visuo-spatial attention show a remarkable overlap in clinical neuropsychology and functional topography (II; III; Corbetta 1998; Corbetta et al. 1993; Corbetta and Shulman 2002; Mesulam 1990; Petit et al. 1999). The primary areas involved include a fronto-parietal network including the frontal eye fields (FEF), supplementary eye fields (SEF), the inferior and posterior superior parietal lobes and visual cortices, and can be illustrated using neuroimaging techniques (II; III; Anderson et al. 1994; Petit et al. 1993; Sweeney et al. 1996). Patients with structural frontal lobe lesions involving the FEF's (Guitton et al. 1985; Paus et al. 1991), and patients suspected of having a dysfunctional frontal lobe function, such as in schizophrenia (Fukushima et al. 1990) have difficulties in maintaining central-gaze fixation with the appearance of peripheral visual stimuli, that is ignoring visual distractors. The functional anatomy in healthy subjects during the same "saccadic suppression" task shows activity in several areas including the fronto-parietal network with a right-sided preponderance (II; Petit et al. 1999). The frontal segments may be involved in active inhibition of the orienting response, while the parietal areas may be involved more in reflexive attentional shifts and encoding of target position in space. During normal conditions the direction of eye movements and attention are tightly related, move in synchrony and select common targets in the visual field. However, eye movement and attention can also be dissociated by reflex or by cognitive strategy, denoted covert attentional shift and orientation, respectively. Some functional imaging paradigms of covert attentional operations (Corbetta et al. 1993; Nobre et al. 1997) involve actively orienting and reflexively shifting attention to a peripheral target while maintaining gaze fixation. These designs may not only reflect attentional processing as increased inhibitory drive used to dissociate gaze and attentional axis can be expected (II). In the performance of overt eye movements, voluntary or visually guided, activity distribution in the fronto-parietal network show a strong overlap with areas that are active when attention is shifted without eye movements indicating a functional relationship between the two neural systems (II; Corbetta et al. 1998; Petit et al. 1999). Furthermore, the activated areas are larger and more symmetrical than in the "saccadic suppression" task. Thus, activity is larger when a target is task relevant. It should be noted that an overlapping network does not rule out a specialisation within regions with different neurons devoted to attentional and oculomotor processing or that neural processes are interdependently shared between systems. This work (II) has been presented in a previous thesis (Law 1997).

PARIETO-OCCIPITAL CORTEX INVOLVEMENT DURING EYE MOVEMENTS IN THE DARK

To further disentangle the extended network of areas involved during saccades, we removed the visual component of the task and asked subjects to perform voluntary eye movements in the dark

(III). This supported the existence in the human brain of non-visual areas in the parietal lobes. These could be involved in encoding spatial location in a head frame of reference (Galletti and Battaglini 1989) that are active in maintaining visual continuity across saccades. Saccades have a detrimentally disruptive effect on perceptual continuity; yet, we are able to experience a coherent and stable visual world. Thus, when tracking a moving object we do not mistake the retinal image shift as a moving world. The general solution, as quoted by Hermann von Helmholtz (1821-94), one of the founding fathers of psychophysics, was that "in order to correctly evaluate sensory signals from the external world, any sensory system must be concurrently informed about the motor activity that modifies the sensory afference" (von Helmholtz 1910). Thus, the retinal image signal must be centrally cancelled out by an eye movement signal. Object motion perception only occurs when these two signals are incongruent. At the time when this was debated there were two theories, the *inflow* theory, signifying that the eye movement signal came from afferent proprioceptive feedback from the eye muscles proposed by sir Charles Sherrington (1857-1952) (Gregory 1977). Sherrington theory was probably influenced by his work on the spinal reflexes. He is known in the neuroimaging community, together with Charles Roy, for suggesting a coupling between regional cerebral metabolism and rCBF (Roy and Sherrington 1890). Another understanding came from von Helmholtz formulated in the *outflow* theory. This hypothesised cancellation, not by proprioception, but by a direct extra-retinal position signal copying the efferent eye movement command, often referred to as corollary discharge ("Das Reafferenzprinzip") (von Holst and Mittelstaedt 1950). The most intuitive evidence for the latter theory came from subjects or patients that have their proprioceptive inflow signal eliminated by paralysis either from curare or from neuropathy. Alone the attempt to initiate eye movements can shift the perceived image. Thus, corollary discharge is related to our ability to predict the outcome of a motor command without delay. Further the *actual* outcome can be compared to the *intended* outcome, which can be used to adjust behaviour in a feed-forward model used in e.g. motor learning (Balslev et al. 2002). Particularly the cerebellum and the parietal lobes have been proposed to be involved in this process (Blakemore and Sirigu 2003). Single-cell recording in the lateral intraparietal cortex (LIP) of the monkey (Figure 6) have revealed neurons that shift receptive fields immediately before an eye movement in order to anticipate the retinal consequences of that eye movement and update the retinal coordinates of remembered stimuli to generate a continuously accurate representation of visual space (Duhamel et al. 1992a). Thus, if it can be predicted that an eye movement will move the image of a bird to a given new retinal location, that image representation will be moved in the brain before light from the bird has

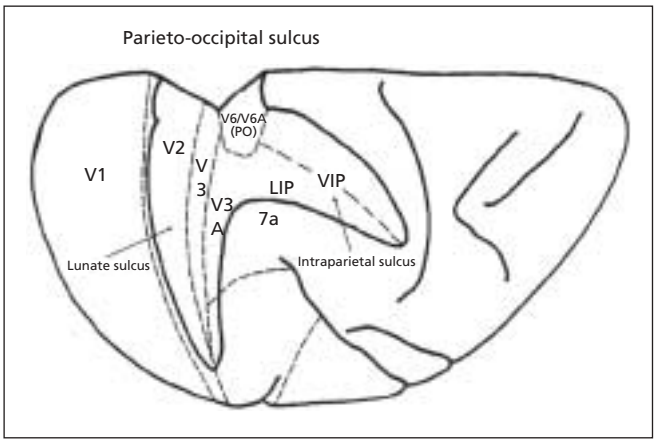

Figure 6. Dorsal view of the right hemisphere of the macaque cortex. The parieto-occipital sulcus, lunate sulcus, and intraparietal sulcus have been opened showing the location of some visual responsive areas. LIP, PO, VIP: see abbreviations. Adapted from (Colby and Goldberg 1999).

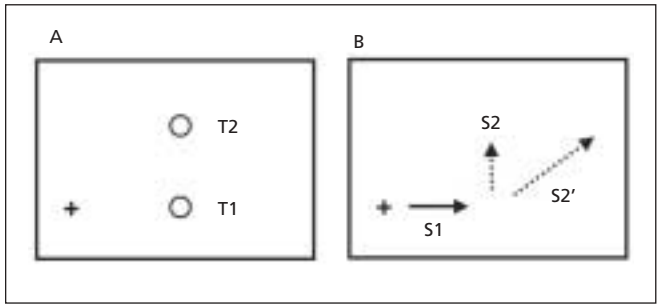

Figure 7. The double-step saccade paradigm. A) during fixation on "+" two visual targets (T1, T2) are flashed in sequence. B) the goal is to perform two saccades in sequence (S1, S2) to the two locations in darkness. The second saccade (S2) cannot be corrected performed without information of the eye displacement of the first saccade (S1). Corollary discharge deficit will usually be manifest by a displacement of the end point of the second saccade (S2') corresponding to the retinotopical position of the second target at the time of spatial encoding erroneously added to the position of the first target.

shifted retinal position. This may function to maintain visual continuity.

The reliance of corollary discharge can be demonstrated clinically using the so-called double-step saccade paradigm (Hallett and Lightstone 1976). Two sequentially and briefly flashed visual targets are presented in the periphery at two different locations. The object is to saccade in sequence and in the dark to the two locations. This creates a spatial dissonance between the retinal coordinates of the second target and motor coordinates of the required eye movement. In order to compensate fully, non-retinal information about the eye movement vector has to be integrate (Figure 7). In patients with parietal lesions only the second saccade is dysmetric, probably because of a corollary deficit. This underlines the importance of the parietal lobes in keeping and updating spatial constancy despite moving eyes and in planning sequential movements (Duhamel et al. 1992b; Heide et al. 1995).

Another factor in stabilizing the world is a suppression of the visual input during a saccade. This mechanism has been found to act early in the visual stream on the colour-blind magnocellular visual pathway and show selectivity for patterns modulated in luminance at low spatial frequencies. This pathway provides the dominant input to motion centres and areas involved with attention (Burr et al. 1994). Behaviourally this can be measured as a peri-saccadic compression of the perceived position of objects in visual space, almost as a deficit in spatial memory (Lappe et al. 2000; Ross et al. 1997). *Involuntary* ocular oscillations in the dark such as caloric nystagmus cause a pronounced deactivation in the striate and some extra-striate cortices (Wenzel et al. 1996). The physiological importance could be to protect the visual cortex ("afferent inhibition") from conflicting input and alleviates the distress of apparent motion of the visual scene (oscillopsia). A similar protective mechanism could be behind the paradoxical deactivation in the occipital lobes during visual stimulation in stage IV sleep (Born et al. 2002) or the deactivation of visual cortex in the early learning phases of mirror tracing (Figure 8).

In mirror tracing a subject follows the path of a star-shaped maze with a computer mouse pointer, but with the visual input mirrored (Figure 9). This creates dissociated and conflicting visual and proprioceptive sensory input (Balslev et al. 2004; Balslev et al. 2002).

Thus, the ocular oscillations of nystagmus cannot be equated with voluntary or reflexive saccades. In accordance we find no evidence of depression in striate areas during voluntary eye movements whether these are performed in the dark (III) or are visually guided. Particularly the latter show widespread and intense increased activity (II; Anderson et al. 1994; Beauchamp et al. 2001; O'Sullivan et al. 1995; Sweeney et al. 1996). Thus, saccadic suppression in the early visual pathway is probably in the form of reduced visual sensitivity (Thilo et al. 2004) and not a complete disruption of the processing of visual information.

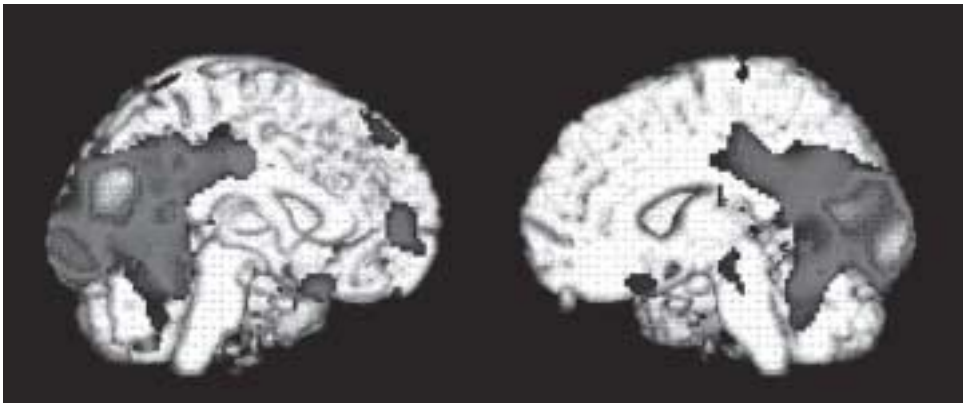

Figure 8. Deactivations in a grey scale in occipital cortex occurring immediately after the onset of mirror tracing. Data derived from (Balslev et al. 2002).

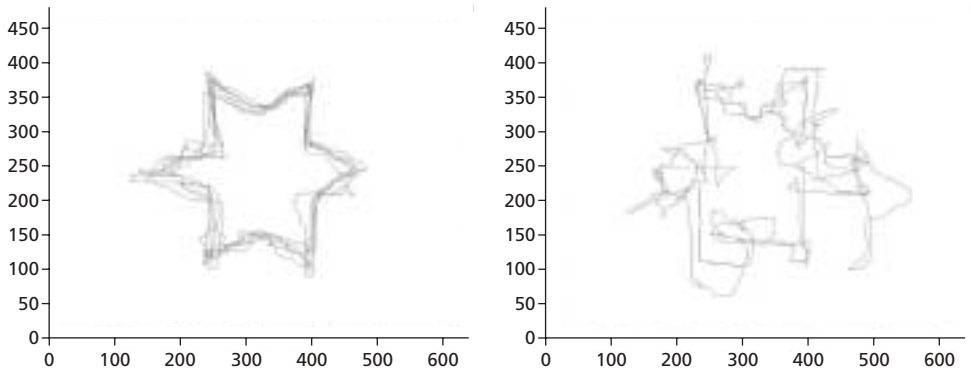

Figure 9. Examples of registered traces performed with a mouse pointer before (left) and immediately after (right) mirroring of the visual input.

Proprioceptive eye muscle impulses continue to play an important role in spatial vision. Visual information is transmitted to the primary visual cortex and most other visual areas of the brain in retinotopic coordinates. The monkey visual cortex seems to use at least two different strategies for the transformation from a retinal reference frame to a body centred reference frame in objective spatial coordinates. The first is a proprioceptive eye-position-dependent encoding system, based on the activity of retinotopically-organized gaze-sensitive visual neurons. This has been described in prestriate cortex, area V3A (Galletti and Battaglini 1989) and V6 (Galletti et al. 1991), and in the intraparietal sulcus, visual areas 7a and LIP (Andersen and Mountcastle 1983; Mountcastle et al. 1975), and might construct *dynamic* spatial maps of the visual environments in the brain continuously updated by changes in the direction of gaze (Figure 6). The second is a system independent of eye position, and based on the discharge of neurons with receptive fields organized in "real-position" craniotopic (head-centred) coordinates, where single neuronal elements physically encode single spatial locations of the visual field. This is partly located in the cortex of the anterior bank of the parieto-occipital sulcus, area V6A, dorsal to V6, and might build *static* maps of visual space, independent of eye position (Galletti and Battaglini 1989; Galletti et al. 1993; Galletti et al. 1995). Similar craniotopic organization thought to have the same function has been found elsewhere in the parietal lobe, e.g. the ventral intraparietal area (VIP) (Duhamel et al. 1997). The benefit of stable spatial encoding is to enable us to plan movement trajectories and reach out to grasp an object without necessarily having the light from that object in a fixed retinal position at all times. The involvement of area V6/V6A in reaching has been documented from single-cell recording studies in the monkey (Andersen and Buneo 2002) and from human brain mapping studies (de Jong et al. 2001). Clinically a lesion to the posterior parietal cortex, including this area, can lead to the symptom of optical ataxia (Seelenlähmung des "Schauen", mind paralysis of vision) a part of the Balint syndrome (Balint 1909). This is manifest as inaccuracy when reaching or grasping visual objects, particularly when immediate, and not delayed, visually guided action is needed (Rossetti et al. 2003), and may be caused by a misalignment in the coordinate transformation from retinal space to a motor programming space (Perenin and Vighetto 1988).

Using topographical electroencephalography the parieto-occipital cortex has shown electrophysiological patterns of activation during the execution of saccades in the dark (Moster and Goldberg 1990; Skrandies and Laschke 1997). Further, on the cellular level neurons in area V6 (former area PO) have been found to increase their discharge rate during eye movements in the dark (Galletti et al. 1991). Thus, the performance of self-generated eye movements in the dark when using neuroimaging methods could be one strategy to locate these and other areas that are either gaze-sensitive or receive corollary discharge. The early PET saccade studies were based on few scans in 4-5 subjects and did not document changes in the parieto-occipital cortex (Petit et al. 1996; Petit et al. 1993). Using PET scanners with increased sensitivity from 3D acquisition, activity increase was found in the cunei along the parieto-occipital sulcus, and in the intraparietal sulci (III; Dejardin et al. 1998), areas that could putatively represent the human homologues of areas V6 (Dechent and Frahm 2003), V3A (Clarke and Miklossy 1990; DeYoe et al. 1996), and 7a/LIP, respectively, that, as noted, have been found to include gaze-sensitive neurons or receive corollary discharge (Figure 6). No activity was found in primary visual areas, even at a lowered significance threshold. Thus, it is unlikely that a signal was relayed initially through the striate cortex consistent with data from single-cell recordings (Wurtz 1969). The functional connectivity between the frontal eye field and the ipsilateral cuneus has been documented using combined PET and TMS. This can be performed without being confounded by overt eye movements, and presumably represent orthodromic spread of activity along known anatomical pathways (Paus et al. 1997). Activation of the posterior bank of the parieto-occipital sulcus is also seen during blinking that also, like saccades, disrupts visual input. It has similarly been proposed to reflect activity of non-visually responsive neurons that are active in maintaining visual continuity across blinks in response to a corollary oculomotor signal (Bristow et al. 2005).

Activation of the cunei can also be found during visually guided saccades, but have been difficult to individualize because of limited resolution and with the spill-over of intense activity in the neigh-

bouring visual cortices (II; Anderson et al. 1994). Using event related fMRI this activity has been more clearly illustrated (Perry and Zeki 2000). Further, head and gaze movements to visually presented targets increase the fMRI signal response in the cunei bilaterally suggesting importance for integration of corollary discharge/proprioception from several sources in the remapping of external space (Petit and Beauchamp 2003). The early fMRI studies during eye movements in the dark do not offer full brain coverage and can, thus, not contribute observations from these areas (Bodis-Wollner et al. 1999; Bodis-Wollner et al. 1997).

One importance of corollary discharge is in assigning the source of incoming sensory signals to one-self or the out-side world, which will activate behavioural sets that are altogether different. Thus, it's not irrelevant if the hand you feel in the back of your neck belongs to you or to somebody else. This is also thought to be the reason why you cannot tickle yourself. Sensations arising from own touch are cancelled, while external touch is not (Weiskrantz et al. 1971). It has been suggested that pathological states such as delusions of control, an example of passivity experiences described in schizophrenia, could arise from a defect of this prediction of state or internal labelling. There is no longer a difference between the internal and the external sensory signals, and efferent copies from all actions, including cognitive and emotional, are misinterpreted or logically rationalized as externally derived, hence, delusions of external control (Frith 1992; Frith et al. 2000).

CONCLUSION

Methods to perform human brain mapping studies using PET and rCBF measures have been implemented and evaluated in behaviours of increasing cognitive complexities ranging from visual stimulation, oculomotor function with related cognition, and language. A new extremely short-lived PET rCBF tracer, $^{10}CO_2$, was implemented, and human data presented for the first time. The feasibility of this tracer for human brain mapping use, and the predicted increase in the number of independent PET scans was proven. Further technical developments are needed before full-scale use. A new two-tissue compartment kinetic model for the quantification of rCBF using $H_2{}^{15}O$ was implemented for the first time in the brain. The deteriorating effects of limited scanner resolution in putative grey matter on quantified rCBF values and activation response was clearly demonstrated. It was validated by stereological measures in monkeys that the fitted volume for the "fast" flow component convey information about the anatomical volume of grey matter, and as expected this fitted volume was unaffected by even large increases in rCBF. The absolute measures, however, was reduced by 40%, perhaps owing to the small difference between the partitions coefficients of water in grey and white matter.

As predicted from the neuropsychological literature it was demonstrated for the first time using neuroimaging techniques that a functional dichotomy exist in the brains of reading Japanese between two scripts systems, Kana and Kanji, later corroborated by other research teams. Our investigations of eye movements revealed the location of the classical oculomotor regions presenting supportive evidence for involvement of these areas in cognition, e.g. eye movement inhibition and directed attention. Further studies revealed activation in the parietal lobes that could be the neural correlate of areas in the monkey involved in maintaining visual continuity during eye movements.

CLINICAL PERSPECTIVE

The clinical aim in the primary surgical treatment of high-grade gliomas is to reduce the tumour burden as much as possible, which in retrospective data have been shown to prolong survival in these patients (Salcman 1985). Cortical mapping allows the neurosurgeon the ability to achieve aggressive resection with the preservation of neurological function. Several papers have in relatively small groups (<25) of adults and children reported on non-invasive functional mapping using rCBF PET or fMRI as a useful tool in the assessment of eloquent brain areas prior to neurosurgical procedures for vascular malformations, epilepsy, and brain tumour resections, allowing detailed preoperative planning. The most robust activation response is identified in Rolandic cortex in relation to motor tasks (Fried et al. 1995; Leblanc and Meyer 1990; Mueller et al. 1996). Some success has also been made with language function (Ashtari et al. 2005; Binder et al. 1996; Gaillard et al. 2004; Herholz et al. 1997; Kaplan et al. 1999; Leblanc et al. 1992; Leblanc et al. 1995; Pardo and Fox 1993) as a non-invasive alternative to the intracarotid amobarbital, or so-called Wada, test (Wada and Rasmussen 1960) for lateralization of the language dominant hemisphere and memory function (Loring et al. 1990). The preoperative visualisation of memory function has been less extensively explored (Golby et al. 2002; Henke et al. 2003; Janszky et al. 2005). The mapping of cognitive function can be variable owing to inadequate patient performance caused by cognitive deficits and effects of medication. Further, the pathological process itself may influence the activation signal, e.g. through an alteration of the neurovascular coupling (Ojemann et al. 1998). Thus, caution in interpretation is warranted particularly for activation foci adjacent to lesions. In conclusion, further developments with emphasis on clinical outcome measures are needed before routine clinical implementation.

Brain mapping techniques could also prove important with the introduction of new radiation treatment modalities by protons or light ions with physical characteristic that allow more precise tailoring of irregular planning target volumes sparring non-target critical nervous structures in the vicinity, and, thus, give better local tumour control with less collateral damage than conventional photon radiation therapy (Baumert et al. 2001; Schiffer 2005).

SUMMARY

Measurement of the regional cerebral blood flow (rCBF) is an important parameter in the evaluation of cerebral function. With positron emission tomography (PET) rCBF has predominantly been quantified using the short-lived radiotracer oxygen-15 labelled water ($H_2{}^{15}O$) and an adaptation of the Kety one-tissue compartment autoradiographic model. The values attained in putative grey matter, however, are systematically underestimated because of the limited scanner resolution. For this reason we applied a dynamic kinetic two-tissue compartment model including a fast and a slow flow component each with a perfusable tissue fraction. In the fast component rCBF was 2-2.5 times greater than grey matter values using traditional autoradiography in both human and monkey. Visual stimulation in human gave a corrected rCBF increase of approximately 40%. Visual stimulation was also used to indirectly validate carbon-10 labelled carbondioxide ($^{10}CO_2$), a new very short-lived rCBF PET tracer with a half-life of only 19.3 seconds. This allowed an increase in the number of independent PET scans per subject from 12-14 using $H_2{}^{15}O$ to 64 using $^{10}CO_2$. The experiment demonstrated a maximal activation response in the visual cortex at a 10-15 Hz stimulation frequency.

The use of the rCBF PET mapping technique is illustrated by studies of the organization of language and the oculomotor system. With respect to the former, we found confirmation of neuropsychological evidence of the involvement of the left supramarginal/angular gyrus in reading in Japanese of a phonologically based script system, Kana, and of the left posterior inferior temporal gyrus in reading of a morphogram based script system, Kanji.

Concerning the organization of the oculomotor system we found overlapping areas in fronto-parietal cortex involved in maintaining visual fixation, and performing visually guided and imagined eye movements. These data show that overt eye movements are not a prerequisite of the activation of classical cortical oculomotor regions and underscore the involvement of these areas in other behaviours such as visual attention and saccade inhibition. During eye movements in the dark an increased activation response in the parieto-

occipital cortex can be found. This can be interpreted as effects of the gaze-sensitive neurons that are used to objectively localize objects relative to the body, and efferent copies of motor commands, used to predict the visual consequences of eye movements to maintain visual continuity. Defect efferent copies are in some neurobiological models of schizophrenia thought to contribute to passivity phenomena.

The clinical perspective of brain mapping techniques is to preoperatively locate eloquent areas, e.g. motor function, language, and memory, allowing the achievement of optimal neurosurgical resection with the preservation of neurological function.

ABBREVIATIONS

ABBREVIATIONS USED IN TEXT:

ARG:	autoradiographic method
$^{10}CO_2$:	carbon-10 labelled carbondioxide
CSF:	cerebral spinal fluid
ED:	effective dose
FEF:	frontal eye fields
fMRI:	functional MRI
$H_2{}^{15}O$:	oxygen-15 labelled water
LIP:	lateral intraparietal cortex
MRI:	magnetic resonance imaging
NEC:	noise equivalent counts
PO:	parieto-occipital area
PET:	positron emission tomography
PVE:	partial volume effect
rCBF:	regional cerebral blood flow
rCMRglc:	regional cerebral glucose metabolism
ROI:	region of interest
S/N:	signal-to-noise ratio
SEF:	supplementary eye fields
TMS:	transcranial magnetic stimulation
VIP:	ventral intraparietal area

ABBREVIATIONS USED IN MATHEMATICAL EQUATIONS:

$\otimes$	convolution operator
$C_a(t)$	arterial input function [Bq•ml^{-1}]
$R(t)$	radioactivity concentration in tissue measured by PET [Bq•ml^{-1}]
f	regional CBF per tissue mass [ml•min-1•g^{-1}]
α	water perfusable tissue fraction [g•ml^{-1}]
p	brain tissue-to-blood partition coefficient of water [ml•g^{-1}]
V_a	arterial blood volume fraction [ml•ml^{-1}]
V_d	the (apparent) volume distribution of water [ml•g^{-1}]
t	time [min]
f_g	regional CBF for gray matter tissue [ml•min-1•g^{-1}]
α_g	gray-matter perfusable tissue fraction [g•ml^{-1}]
p_g	gray-matter-to-blood partition coefficient of water [ml•g^{-1}]
f_w	regional CBF for white matter tissue [ml•min^{-1}•g^{-1}]
α_w	white-matter perfusable tissue fraction [g•ml^{-1}]
p_w	white-matter-to-blood partition coefficient of water [ml•g^{-1}]

THIS DOCTORAL THESIS IS BASED ON THE FOLLOWING PUBLICATIONS:

I. Law I, Kanno I, Fujita H, Lassen NA, Miura S, Uemura K. (1991) Left supramarginal/angular gyrus activation during reading of syllabograms in the Japanese language. J Neurolinguistics 6:243-251

II. Law I, Svarer C, Holm S, Paulson OB. (1997) The activation pattern in normal humans during suppression, imagination and performance of saccadic eye movements. Acta Physiol Scand 161:419-434

III. Law I, Svarer C, Rostrup E, Paulson OB. (1998) Parieto-occipital cortex activation during self-generated eye movements in the dark. Brain 121:2189-2200

IV. Iida H, Law I, Pakkenberg B, Krarup-Hansen A, Eberl S, Holm S, Hansen AK, Gundersen HJ, Thomsen C, Svarer C, Ring P, Friberg L, Paulson OB. (2000) Quantitation of regional cerebral blood flow corrected for partial volume effect using O-15 water and PET: I. Theory, error analysis, and stereologic comparison. J Cereb Blood Flow Metab 20:1237-1251

V. Law I, Iida H, Holm S, Nour S, Rostrup E, Svarer C, Paulson OB. (2000) Quantitation of regional cerebral blood flow corrected for partial volume effect using O-15 water and PET II. Normal values and gray matter blood flow response to visual activation. J Cereb Blood Flow Metab 20:1252-1263

VI. Law I, Jensen M, Holm S, Nickles RJ, Paulson OB. (2001) Using (10)CO2 for single subject characterization of the stimulus frequency dependence in visual cortex: a novel positron emission tomography tracer for human brain mapping. J Cereb Blood Flow Metab 21:1003-1012.

The publications are referred to in the text by the above Roman numerals.

Publication II has previously been presented in a separate thesis (Law 1997).

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