The diagnostic value of PET metabolism imaging in patients with traumatic brain injury

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Abstract

Background: Structural imaging (MRT/CT) is usually used as the first method to diagnose the presence or absence of traumatic brain injury (TBI). However, some studies show that in some cases abnormalities are missed when using structural imaging. The question arises whether the use of functional imaging techniques has additional value at all. For the functional imaging techniques, Single Positron Emission Computerized Tomography (SPECT) and Positron Emission Tomography (PET), the accuracy of detecting TBI by SPECT imaging has already been examined, of PET it has not. This thesis covers an evaluation of a possible role of PET-imaging in the diagnosis and possible clinical outcome of traumatic brain injury. The first study contains a literature review to evaluate the accuracy role of PET-imaging in the diagnosis of TBI. In a second section, a study is performed to determine a possible clinical value of PET-imaging in tracing a correlation between hypo glucose metabolic activity in specific brain areas and cognitive impairments.

Methods: In the first study a literature search was performed with the use of the databases Psychinfo and Pubmed to identify relevant studies for assessing the accuracy of the PET scanning technique. The imaging method should identify abnormalities in TBI patients, however without missing abnormalities, and nor suggesting abnormalities where they are not; i.e. the method should be accurate.

The second study: in a retrospective study eight patients with mild TBI were tested in the chronic phase of TBI. Neuropsychological assessments were examined and regional cerebral glucose metabolism at rest was measured with Fluordeoxyglucose-PET to find possible correlations.

Results: 25 studies, out of an evaluation of 45 studies proved to be relevant and showed that PET-imaging is superior to structural imaging with a sensitivity of 97% for PET-imaging, against 44% for structural imaging. Despite this superiority in sensitivity of detecting TBI, previous studies suggest that PET-imaging has no predictive value with regard to the development of, and recovery from TBI. This suggestion may not be valid as the used studies showed a large heterogeneity in methods applied and in patients' characteristics. Insufficient information was available on the effects of tracer used, time elapsed between injury and imaging, method of comparison between abnormal and normal tissue areas, degree of severity of TBI and age of the patient.

The main outcome of the second study is that all the patients in the investigated group that had been tested showed at least one abnormal hypo-glucose metabolism in the frontal region, the parietal region or the subcortical regions. No abnormalities were found in other regions, such as the cingulate cortex. Due to the small number of participants, a correlation analysis gave no significant results.

Conclusion: To determine the best method for detecting abnormalities as well as the predictive value of PET imaging prospective, repeated and simultaneously taken structural and functional imaging need to be compared.

Although in the second study a clear distinction was made with regard to mild TBI, the chronic phase of injury and the used method of combining brain regions into larger domains the number of data was too small to conduct a correlation analysis. Further research with a larger sample size and with the use of a standardized method and no difference in method and patient characteristics is essential.

Table of Contents

General Introduction

The use of structural imaging (MRI/CT) is standard medical practice to diagnose the presence or absence of traumatic brain injury (TBI). However, in some cases abnormalities are missed when using structural imaging (Chen, Kareken, Fastenau, Trexler, & Hutchins, 2003); Shiga et al., 2006 ;Mattioli et al., 1996; (Fontaine, Azouvi, Remy, Bussel, & Samson, 1999). The question arises whether the use of functional imaging techniques contains added value. Of the functional imaging techniques (Single Positron Emission Computerized Tomography and Positron Emission Tomography), the accuracy of detecting TBI by SPECT imaging has already been examined (Jacobs, Put, Ingels, Put, & Bossuyt, 1996). PET, however, has received less attention.

This study contains a literature review to evaluate the possible role of PET-imaging in the diagnosis of TBI. In a second section, a study is performed to determine a possible clinical value of PET-imaging in tracing a correlation between activity in specific brain areas and cognitive impairments.

Traumatic Brain Injury

In the United States 1.5 million people suffer from traumatic brain injury (TBI). Annually it results in over 50.000 deaths, 300.000 hospitalizations and 80.000 to 90.000 individuals with long-term disability. The estimated costs are over 60 billion dollars (Dubroff & Newberg, 2008). In Europe brain injury accounts for one million hospital admissions per year (http://www.internationalbrain.org).

Traumatic brain injury is caused by an external physical force to the brain. The external force can cause a deformation of the inner brain within the rigid skull. These forces may produce primary and secondary injury. The primary injury patterns include focal contusions, hematomas and diffuse injury. This may initiate a complex sequence of events, causing secondary damage; ischemia, cerebral swelling, axonal injury, inflammation and regeneration (Zasler, Katz, & Zafonte, 2007).
The brain is able to recover from damaged functions and damaged brain areas. The responsible processes, “sprouting” (newly developing connections between neurons) and “neuro-genesis” (newly created neurons), probably start within the first months (Zasler, et al., 2007).

In most cases with severe TBI, the trauma as such is clearly diagnosed, but the morphological and functional effects of the trauma are hard to recognise. TBI is not a one time event but a process. The development of both primary and secondary injury can result in neuropsychological or neuropsychiatric problems related to cognitive domains of concentration, attention and memory. Besides these, changes in mood, behaviour and personality are commonly seen. The social consequences of TBI can be considerable; increased risk of suicide, divorce, chronic unemployment and economic strain. Also depression, social isolation and anger are common secondary problems (Zasler, et al., 2007).

The severity of TBI can be estimated by the level of consciousness in time (post traumatic amnesia) and/or measurements of the Glasgow Coma Scale. The clinical outcome can be retrieved from the clinical record and a clinical interview with the patient and close relatives. Neuropsychological and neuropsychiatric symptoms can be revealed by taking several tests (STROOP-colour word task, IQ-

task e.g.) and questionnaires (Beck Depression Inventory, Minnesota Multiphasic Personality Inventory). Symptoms observed after TBI should ideally be compared with those of the premorbid functioning of the patient. However, these are often not available. Test results of post-TBI are therefore usually compared with normative data of a representative population with regard to the patient (age and education) (Bazarian, Blyth, & Cimpello, 2006).

Detecting Traumatic Brain Injury

Numerous imaging methods exist, but a limited number of them have clinical potential (Belanger, Vanderploeg, Curtiss, & Warden, 2007). There are structural and functional cerebral imaging methods. Structural image techniques are MRI, and CT. Functional imaging techniques are SPECT, PET and fMRI.

Structural methods visualize the abnormality in tissue of the brain, usually based on differences in tissue density. The structural imaging techniques define the morphological effect of TBI. Of most of the moderate and severe TBI patients a structural cerebral brain scan is taken to detect or indicate the need for acute surgery in cases as skull fractures and hematomas. Repeated scanning may be necessary to monitor bleedings and swellings.

Functional imaging techniques visualize the changes in physiology of the brain. This is based on the fact that metabolism in living cells requires oxygen and glucose, which are supplied by the blood flow. Functional imaging techniques visualize a combination of physical damage and its functional effects.

Further details of these imaging techniques are presented in Appendix 1.

Study 1 | Diagnostic value of Positron emission Tomography (PET) metabolism imaging in patients with Traumatic Brain Injury: a meta-analysis of accuracy.

1.1 Introduction

The risk of TBI is not equally divided among the population. Adolescents, young adults and persons older than 70 years have the highest risk of TBI. Traffic accidents are the main cause of TBI. As well as falling, accidents at home, sports accidents, accidents at work and suicide attempts.

The overall outcome of reviews of neuroimaging in cases of TBI, is that structural techniques are mainly used in emergency settings, usually CT-scanning, to detect possible skull fractures. During follow-ups, apart from MRI, functional imaging techniques are used to explain post-concussional symptoms (secondary brain injuries) and/or to predict outcome for research.

Several studies (Chen, et al., 2003; Shiga *et al*. 2006 ;Mattioli *et al*., 1996; Fontaine, et al., 1999) state that structural neuroimaging sometimes fail to detect abnormalities in patients with neuropsychological and cognitive deficits, especially in cases with mild TBI. This often raises controversy about the possibility of an organic base of symptoms.

To relate physical brain abnormalities to neuropsychological or neuropsychiatric complaints, a suitable and accurate image technique of the brain is required. The imaging technique should only identify abnormalities in TBI patients (sensitivity) and not in healthy patients (specificity); the detected abnormalities must be relevant. Once a useful imaging method is identified, the search for relations between symptoms and brain images can start.

Ruff *et al.* (1994) presented neuropsychological and PET scan data on six head injury cases. All persons had minor abnormalities or none on the CT or/and MRI. They suggest that there will be a dilemma when neuropsychological tests are positive whereas the results from the neuroimaging techniques are negative. Although neuropsychological tests have proven to be as sensitive as CT (Lezak, Howieson, & Loring, 2004), there always exists an element of doubt about the validity of neuropsychological findings due to the subjectivity of behavioural measurements. Neuropsychological assessments are criticized because measurements of cognitive functioning may be influenced by the patient's cooperation, motivation, mood fluctuation or even pre-existing cognitive limitations. Ruff, et al. (1994) suggest that PET may offer an objective and dynamic method in order to delineating dysfunctional brain processes. Langfitt *et al*. (1986) reported in three cases that PET provided superior information compared to CT. They noted in all three cases a discrepancy between the CT findings (negative) and the neuropsychological and PET-data (positive cerebral dysfunction). They suggest that PET apparently has a potential of being more sensitive, not only in terms of a finer resolution, but primarily because of its functional analyses. They concluded that it is important to study larger samples to classify different clusters or patterns of pathophysiology related to patterns of deficits in everyday functioning.

In SPECT studies it was already suggested that this method of functional imaging reveals a higher sensitivity compared to structural imaging and is superior in determining the predictable clinical outcome. Jacobs, et al. (1996) investigated a group of patients with mild traumatic brain injury with a normal structural imaging. SPECT imaging and clinical assessment were performed. After four weeks re-evaluations were made at three different times; 3, 6 and 12 months after brain injury. During all follow-up evaluations the sensitivity, specificity, positive predictive value and negative predictive value (see below) were calculated. The sensitivity and Negative Predictable Value (NPV) of SPECT were high at all evaluations and increased in the second evaluation (6 months) up to 100%. The negative predictive value and specificity however remained low both at an evaluation after 3 months as well as after 6 months. These values increased to 85% and 83%, respectively, but not until twelve months after. This suggests that a normal SPECT-scan is a reliable tool in the exclusion of clinical consequences of mild traumatic brain injury. Another outcome is a positive SPECT-scan at 12 months post-injury is a reliable predictor for clinical outcome.

In a review of Wiersma *et al*. (presented at World Brain Injury Congress, 2008 Lisbon) the accuracy of all SPECT studies (nearly all retrospectively) was calculated. Seventy-three studies were generated; 31 studies provided sufficient information to define the sensitivity and nine studies to define the specificity, PPV and NPV. Despite the large variability in methods used between the studies, the meta-analyses showed that the sensitivity (78.1%) and NPV (72.5%) of SPECT were much higher than with structural imaging (respectively 39% and 53%). However, specificity and PPV of SPECT were lower than of structural imaging.

The question arises whether this outcome can also be determined with the use of other functional neuroimaging techniques? Like PET, where the glucose metabolism plays an important role rather than perfusion.

PET imaging in TBI patients

Positron emission tomography relies on emissions from radio labelled, naturally occurring substance such as glucose and oxygen that are injected intravenously to produce 2-D imaging. PET imaging is more versatile than SPECT and produces more detailed images with a higher degree of resolution, particularly of deeper structures. A disadvantage is that PET imaging is more expensive compared to SPECT imaging and many hospitals are not equipped for taking PET-scans because there is no cyclotron nearby available to acquire the radio labelled tracer (Bazarian, et al., 2006).

Tracers

The most frequently used tracer to detect regional glucose metabolism (CMRglc) is fluorine-18 labelled fluorodeoxyglusose (FDG). Glucose metabolism as well as other tracers like oxygen-15 labelled H_2O^{15}, $C^{15}O$ and $^{15}O_2$, provide information for obtaining PET images of cerebral blood flow (CBF), cerebral blood volume (CBV), oxygen extraction fraction (OEF) and cerebral metabolic rate of oxygen ($CMRO_2$). H_2O^{15} and $C^{15}O$ can determine the CBF and CBV. After injection of these oxygen tracers an injection of ^{15}O can determine the OEF and the cerebral metabolic rate for oxygen

($CMRO_2$). Other tracers are calcium (^{55}cobalt)^{91} and GABA-A receptor (flumazenil). The pharmacokinetics of the tracers differ and often require an interncyclotron. For example: ^{15}O has a half-life time of only 2 minutes and FDG of about 30 minutes (Dubroff & Newberg, 2008).

Impeding factors

There are numerous factors that influence the PET-imaging, varying from the patients' characteristics to the filtering data. General or regional hemodynamics depend on the time of the day, patients anxiety, attention, blood pressure, arterial carbon dioxide levels, sugar levels, age and gender. Raw data is influenced by the pharmacokinetics of the tracer, the dose of the tracer, the scanner, the scanning conditions, the position and the motion of the patient. This raw data is transformed into a visual brain metabolism image. There is a large variability in results due to differences in processing and reconstruction techniques. It is invalid to compare images and to compute statistical analysis as they are acquired with different processing protocols

1.2 Aim

There are several reviews on brain injury and neuroimaging (Belanger, et al., 2007; Dubroff & Newberg, 2008; Gallagher, Hutchinson, & Pickard, 2007; Le & Gean, 2009; Lee & Newberg, 2005; Metting, Rodiger, De Keyser, & van der Naalt, 2007; Newberg & Alavi, 2003). These studies give an overview of the current imaging techniques in terms of their ability to reveal structural or functional brain abnormalities in patients with head injury. However, none of these reviews discusses the accuracy of the methods. Therefore, the aim of this review is to calculate the accuracy aspects of PET imaging in patients with TBI.

1.3 Methods

In order to find out how PET relates to other techniques in discriminating TBI and non-TBI, studies obtained by literature search were screened on the accuracy of the PET scanning technique. The imaging method should identify abnormalities in TBI patients, should not miss abnormalities, and must not suggest abnormalities when they are absent; i.e the method should be accurate.

Accuracy of methods to detect TBI

The accuracy of a method lies in the ability to distinguish healthy from non-healthy persons. Accuracy can be divided into sensitivity, specificity, positive predictable value (PPV) and negative predictable value (NPV).

1. Sensitivity indicates the percentage of all TBI patients which are detected by the imaging technique (true positive divided by total number of TBI patients).
2. Specificity refers to the proportion of patients without TBI who are correctly classified by the model as healthy.
3. The PPV is the percentage of abnormal brain imaging corresponding with imaging of patients with TBI (true positives divided by the total number of TBI diagnoses).
4. The NPV is the percentage of the normal brain images by the healthy persons (the total true negative divided by the total number of negative diagnoses) (table 1).

Table 1 *Accuracy calculation*

		Patient's condition		
		TBI	**Healthy**	
	Abnormal	True positive (TP)	False positive (FP)	Positive predictive value (PVV)
Brain Image	**Normal**	False negative (FN)	True negative (TN)	Negative predictive value (NPV)
		Sensitivity	Specificity	Accuracy

Accuracy can be defined with use of the sensitivity, specificity, positive predictive value (PVV) and negative predictive value (NPV). Sensitivity = TP/(TP+FN), Specificity = TN/(TN+FP), PPV = TP/(TP+FP) and NPV = TN/(TN+FN)

A literature search on these four accuracy criteria studies was conducted in September 2009. The studies were initially identified from Medline en Psychinfo databases using synonyms for the search terms: *positron emission tomography* OR *PET* OR *PET-scan* AND *traumatic brain injury* OR *TBI* OR *traumatic head injury* OR *brain trauma* OR *head trauma*.

Reference lists were searched for additional studies. The results were filtered on relevance, regarding title and abstract.

1.4 Results

The search revealed 218 respectively 256 hits in Medline and Psychinfo. After exclusion of double hits the studies were screened on title and abstract and 45 studies on PET imaging in patients with TBI appeared to be relevant. Twenty studies are reviews of traumatic brain injury and neuroimaging, the remaining 25 studies are used in the analysis and are summarized in table 2.

Table 2 *Evidence Table*

Study	D[1]	N[2]		S[3]	T[4]	Tracer[5]	Compare			Outcome		Accuracy			
		TBI	C				Method[6]	Region[7]	Structural	Structural	NPT[8]	Sens	Spec	Pvv	Npv
(Alavi, 1989)	-	28	-	-	<1	F	-	C	MRI/CT	-	-	-	-	-	-
(Alavi, et al., 1997)	r	29	-	OS	0.1-5.5	F	ROI L	C	MRI/CT	29/29	-	-	-	-	-
(M. Bergsneider, et al., 1997)	-	28	-	S	<1	F	ROI	H	CT	28/28	-	-	-	-	-
(Marvin Bergsneider, et al., 2001)	r	13	-	MOS	<1.2	F	ROI	G/W		-	-	-	-	-	-
					3-5					-	-	-	-	-	-
(Chen, et al., 2003)	-	5	5	M	>3	F H	ROI	Ca	MRI/CT	0/5	5-5	-	-	-	-
(Coles, et al., 2009)	r	14	10	S	<0.1	H C O	S /ROI L	H	MRI	14/14	-	-	-	-	-
(Crossley, et al., 2005)	C	1	10	S	1	F	S	H		-	1/1	1/1	-	-	-
					12					-	1/1	1/1	-	-	-
(de la Cueva, et al., 2006)	P	55		S	3-9	F	-		MRI	60%		-	-	-	-
(Cunningham, et al., 2005)	R	14	-	S	<0.1	H C O	S /ROI L	H	MRI	14/14	-	-	-	-	-
(Fontaine, et al., 1999)	R	13	6	S	1-12	F	ROI	H	MRI	0/13	13/13	-	-	-	-
(Gross, Kling, Henry, Herndon, & Lavretsky, 1996)	R	20	31	MO	12-60	F	ROI	H	CT	2/20	20/20	20/20	-	-	-
									MRI	0/20	20/20	20/20	-	-	-
(N. Hattori, et al., 2003)	-	16	18	MOS	<0.1	H C O	ROI L	H	CT	16/16	-	-	-	-	-
(Naoya Hattori, et al., 2003)	P	23	17	S	<0.1	F	ROI	H	MRI/CT	23/23	-	-	-	-	-
(Jansen, et al., 1996)	-	5	-	S	<1	Co	ROI	C	MRI/CT	3/5	5/5	5/5	-	-	-
(Kato, et al., 2007)	-	36	30	OS	>6	F	S	H	MRI	-	36/36	-	-	-	-
(Kawai, Nakamura, Tamiya, & Nagao, 2008)	-	15	13	MOS	<1	C O	ROI L	H	CT	15/15	-	-	-	-	-
(Langfitt, et al., 1986)	-	3	-	S	<1	F	ROI	C	MRI/CT	3/3	3/3	3-3	-	-	-
					>6				MRI/CT	2/2	2/2	2-2	-	-	-
(Nakashima, et al., 2007)	-	12	16	-	3-71	F	3D-SSP	H	MRI/CT	-	12/12	10-12	16/16	10-10	16/18

Study	D[1]	N[2]		S[3]	T[4]	Tracer[5]	Compare			Outcome		Accuracy			
		TBI	C				Method[6]	Region[7]	Structural	Structural	NPT[8]	Sens	Spec	Pvv	Npv
(Nakayama, Okumura, Shinoda, Nakashima, & Iwama, 2006)	-	52	30	OS	>6	F	S	H	MRI	-	22/22	-	-	-	-
(Mattioli, et al., 1996)	C	1	25	S	24	F	ROI	H	MRI/CT	0/1	-	1-1	-	-	-
(Rao, et al., 1984)	-	5		S	3-24	FM	-	-	CT	5/5	5/5	5-5	-	-	-
(Ruff, et al., 1994)	-	6	18	MOS	29-59	F	-	H	CT	4/6	6/6	6-6	-	-	-
(Shiga, et al., 2006)	P	10	10	-	>12	O FMZ	ROI	H	MRI	0/10	-	10-10	-	-	-
(Umile, Sandel, Alavi, Terry, & Plotkin, 2002)	R	20	-	M	1.5-93	F	-	-	CT/MRI	5/20	19/20	17/19	0/1	17/18	0/2
(Yamaki, et al., 1996)	-	5	20	S	2-16	F H C O	ROI	G/W	CT/MRI	5/5	-	5-5	-	-	-
					5-21							3-4	-	-	-

Note: [1]Design Study: R stands Retrospective, P for Prospective, C for Case study. [2] Number of participants and healthy controls (c). [3] Severity of TBI: M for mild, O for moderate, S for severe. [4] Time since injury mentioned in months. [5] Tracer used: F for FDG, O for ^{15}O, H for H_2O^{15}, C for C^{15}, [6] Method of comparison: S for SPM, ROI for region of Interest, L for Lesion. [7] Reference Region: H for healthy controls, C contra lateral, G/W for Grey-White matter, Ca for Calcarine cortex [8] NPT: neuropsychological test.

Patients Characteristics

In the 25 generated studies a total of 429 participants and 259 of controls were included. For an interpretation of the studies caution is required as some studies include the same groups of participants in varies studies published. Probably there are research groups who use the same dataset in different studies with different aims like the group of Los Angeles, California (Marvin Bergsneider, et al., 2001; Naoya Hattori, et al., 2003), a group of Gifu, Japan (Kato, et al., 2007; Nakashima, et al., 2007; Nakayama, et al., 2006) and a group of Cambridge, UK (Coles, et al., 2009; Cunningham, et al., 2005).

Table 2 shows a large heterogeneity between the studies. The patients' characteristics vary in severity of TBI and also in time between the onset and the PET imaging. The severity of the TBI difference between the groups of patients varies from mild, moderate to severe. Most studies used the data of groups of patients with severe TBI (12 out of 25 studies). Two of the 25 studies used a group with mild TBI and none of the studies used the data of patients with moderate TBI. Three studies did not mention the severity of TBI of the patients. The remaining eight studies used PET data of patients with a combination of different severity classes of TBI.

Another noticeable difference between the studies is the time elapsed between TBI and the post-injury PET imaging. It varies between acute and chronic phase (less than 72 hours and up to 93 months) post-injury. Of the 25 studies four included repeated PET imaging. Eleven studies included patients with PET scan less than three months post-injury. Fourteen studies refer to patients with a post injury scan of more than three months, eight out of these fourteen studies refer to patients with more than six months post injury imaging. The remaining four studies made use of intermediary data of time post injury PET imaging (0.1-93 months).

Differences in methodologies

A large heterogeneity exists between the 25 studies with regard to the methodology used. For instance the design of the studies varies widely. Excluding the case studies (2), only three out of 25 studies were performed prospectively. Seven studies were undoubtedly performed retrospectively. Thirteen studies did not mention what design was used.

Another difference between the methodologies is the characterisation of the metabolism. Most studies used methods of Huang, et al. (1980) or Sokoloff, et al. (1977) to determine regional Cerebral Metabolic Rate (CMRglc or $CMRO_2$). Because most patients had never had a PET-scan before they became injured, abnormality of metabolism had to be determined by comparison with the metabolism of healthy controls and/or by comparison to posttraumatic metabolism of different brain structures. A semi-quantitative method is to establish differences in metabolism between Region Of Interest (ROIs). Sixty percent of the studies used this method. ROIs can be predetermined by using Brodmann areas or Talaraich Atlas, or ROIs can be determined by comparing areas with lesions to areas with non-lesions. Out of the fifteen studies, in 63% the areas were determined with the aid of atlases. In the remaining 37% of the studies, the areas with lesions were determined by comparing them with regions

with known non-lesions. To identify abnormal metabolism in the determined ROIs, the metabolism can be compared with other not damaged post injury brain structures within the patient (like contralateral or non-lesions in six of the fifteen studies) or compared with ROIs of healthy controls (in nine studies; 60 %)

Where ROIs are semi-quantitative computerized or qualitative studies, Statistical Parametric Mapping (SPM) is a quantitative computerized comparison of the whole brain metabolism. This method of comparison was used in six studies. One study established the cortical activity of each subject's PET image sets, by using 3D stereotactic surface projection (3D-SSP). The remaining studies did not mention the method of comparison.

Different PET tracers were used in the studies. Most studies (17) made use of FDG tracer, which measures the rate of glucose metabolism (CMRglu). Utilization of oxygen or oxygen metabolism can be measured with the use of radioactive oxygen (^{15}O). Three studies used the ^{15}O as well as other labelled oxygen tracers like H_2O^{15} and $C^{15}O$. H_2O^{15} and $C^{15}O$ determine the Cerebral Blood Flow (CBF) and Volume (CBV). After injection of these oxygen tracers, an injection of ^{15}O can determine the Oxygen Extraction Fraction (OEF) and the cerebral metabolic rate for oxygen ($CMRO_2$). In one study only the tracers $C^{15}O$ and ^{15}O (not H_2O^{15}) were used. In another study, a part from the two oxygen $C^{15}O$ and ^{15}O, a (^{11}C Flumazenil) FMZ tracer was used as a marker for neuronal viability. One study used both the oxygen tracers as well as the glucose tracer. The remaining two studies used a calcium tracer (Co) as well as a fluormethaan labelled tracer (FM).

Accuracy outcome

In table 3 the accuracy results are summarized. Most of the studies did not mention the accuracy itself, but provided sufficient information to calculate this. The accuracy was calculated as table 1 shows by totalizing all patients or controls who have had a PET scan, and by totalizing the abnormal and normal PET-scans.

Table 3 *Accuracy of functional imaging*

	Sens	**Sens**		**Spec**		**PVV**		**NPV**		**Severity**		
	Total	<1 month	>1 month	<1 month	>1 month	<1 Month	>1 month	<1 month	>1 month	Mild	Mod	Severe
PET	96% (86/90)	100,00% (9/9)	95% (77/81)	-	94% (16/17)	-	96% (27/28)	-	80,00% (16/20)	90% (17/19)	-	100,00% (26/26)

Note: ()are the total of patients with TBI

Of the 25 studies only eleven studies provide sufficient information for calculating the sensitivity by PET imaging by TBI. One study used repeated imaging (< 1month and an imaging > 1 months). This means that data of 90 out of the 429 patients (table 2) provided sufficient information for calculating a total sensitivity of 96%. These eleven studies did not mention the sensitivity value itself, but give enough information to calculate this. Only two studies provide information of the control group, which

offers the opportunity to calculate the specificity, PPV and NPV (see table 3). The remaining thirteen studies do not provide sufficient information to calculate the sensitivity, specificity, PPV and NPV. Table 3 shows the missing data and specified the sensitivity in different characteristics; elapsed imaging time post-injury and the severity of TBI.

In comparison, 18/25 studies mentioned for each patient the structural outcome. Of these eighteen studies nine studies did also mention the PET outcome for each patient. Of these nine studies, two studies included patients with no structural abnormalities (one case study), and resulted in a sensitivity of 0%. These two studies were therefore excluded from the comparison of sensitivity. One study used repeated structural and functional imaging (< 1month and an imaging > 1 month). This means a total of 65 functional imaging outcome of patients in comparison with 66 structural imaging outcome of patients provided enough information to calculate the sensitivity.

Figure 1 shows a sensitivity of 97% for PET imaging and a 44% sensitivity for structural imaging. This is statistical significant with a non-parametric chi x chi analysis χ^2 (1, N = 131) =43.97, p < .0005. Unfortunately, these studies provide insufficient for making a distinction between the degree of severity and elapsed time between injury and brain imaging.

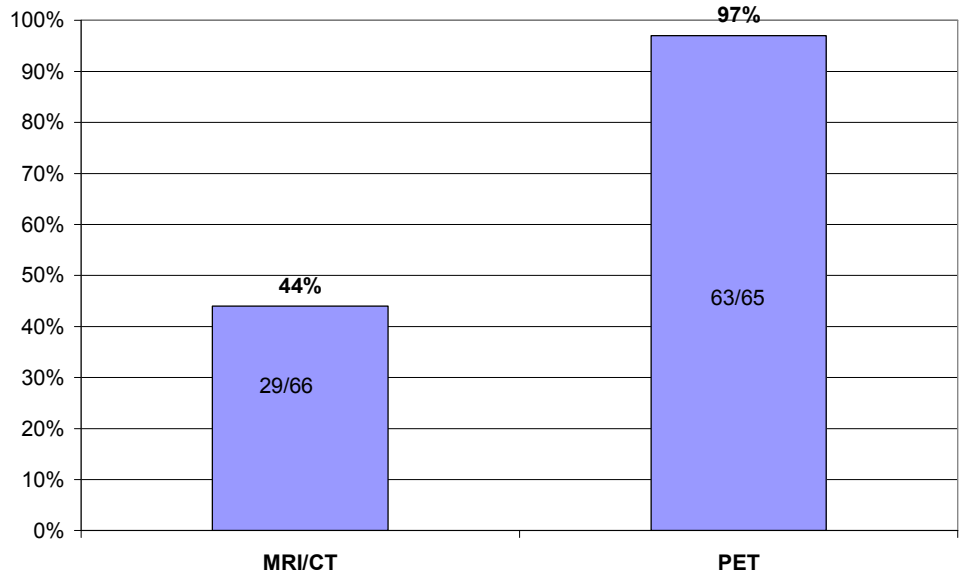

Figure 1 *Comparison of the sensitivity between structural and functional imaging*

1.5 Discussion

The aim of this review is to calculate the accuracy of PET imaging in patients with TBI. In a previous study of (Jacobs, et al., 1996) it is suggested that SPECT imaging has a large accuracy compared to structural imaging methods of patients with TBI. While PET imaging has a more sensitive spatial resolution in comparison with SPECT, the hypothesis is that PET-imaging is (also) more accurate in detecting TBI compared to structural imaging.

The results in table 3 suggest that PET-imaging has a total sensitivity of 96%. This is calculated from all PET data of patients included in the studies and not in comparison with structural imaging. In comparison with structural imaging the total number of patients is lower (66 patients in stead of 90 patients) but even then the sensitivity is almost equal (97%). This is significant considerably higher than MRI/CT imaging (96% respectively 44%) and therefore superior.

Regarding the specificity, PVV and NPV, only figures of data of PET-imaging are available so they cannot be compared with those of structural imaging. Both specificity and PPV of PET imaging seems to be high (94% and 96%). The NPV is 80%, suggesting two out of ten healthy patients is abusively diagnosed with TBI (false negative).

Specificity and sensitivity depend on the diagnostic instrument and decision criterion to determine the normal versus abnormality. The diagnostic instrument is the PET-imaging (or MRI-imaging) and the decision criterion is the determined brain injury mainly based on the patient's complains and cognitive impairments. The PPV and NPV are dependent on the prevalence and diagnostic instrument. Caution is required in using these results as the number of patients in the studies may be too low and thereby the missing data of control persons, limits the drawing of solid conclusions. However, the high sensitivity of PET-imaging compared to structural imaging seems to be superior and may be significant.

Future research

Some previous studies suggest also that PET-imaging may be quite accurate but express doubt about the predictive value for clinical use and treatment. This doubt may not be justified because a large heterogeneity in methods and within the patient groups existed. This may have blurred the outcome of these studies.

Future research

Some previous studies suggest also that PET-imaging may be quite accurate but express doubt about the predictive value for clinical use and treatment (Bergsneider et al, 2001; Yamaki et al, 1996). Caution is required by interpreting the results of this doubt because a large heterogeneity in methods and within the patient groups existed. This may have blurred the outcome of these studies.

Uncertain are the effects of tracer used, time elapsed between injury and imaging, method of comparison abnormal and normal tissue areas, degree of severity of TBI and age of the patient (recovery potential).

Comparison of normal and abnormal brain areas

The best way to identify abnormalities with PET imaging of a TBI patient is to compare the imaging with a pre-traumatic metabolism pattern of the same person. In practise however these are not available. One alternative way is to compare a possibly damaged area with other brain areas of the patient. Areas mostly used are the cerebellum, the contralateral hemisphere and the average metabolism of the whole brain. Caution is required when interpreting these results because it is never certain whether the reference region is normal. Another method is to compare patients' tissue with brain tissues of healthy persons. This requires a standardization of normal brain tissue images. Difficulties can arise when the brain volume or the brain area of the patient diverges from control persons, for instance due to the structural damage itself. If the standardization is based on ROI's, the method is rather subjective; when control persons are used, as well as with the use of reference brain tissue of the patient self. Both establishing differences between functional activity maps and establishing differences between relative sizes, shapes and placements of the ROIs, are subjective and arbitrary (Nakayama *et al.* 2006).

Statistical Parametric Mapping (SPM) seems to be a better and a quantitative method of analysis, since it avoids subjectivities as it defines foci with statistical significant differences with regard to the whole brain. However the method is affected by brain atrophy which forms a disadvantage. To overcome this Nakashima, et al. (2007) suggested the 3D-SSP method which is programmed to avoid these effects. Future research is needed to evaluate the best method.

Tracer

Most PET scans were performed with the use of the tracer FDG. The second tracer used is the oxygen tracer and some studies used both tracers. Oxygen tracer has a shorter half time in comparison with the FDG tracer and can therefore only be used in clinical settings in which an intern cyclotron is present (Bazarian, et al., 2006; Belanger, et al., 2007). Comparison of brain tissue with different tracers is invalid because differences in pharmacokinetics occur.

For instance, Chen, et al., (2003) showed no effect when using the FDG tracer in the resting state of the patient, compared with a control group. In an activating state the oxygen tracer showed a smaller increase in rCBF compared with the control group; however there was no difference in performing with regard to the memory task. The patients had a normal structural scan and were relatively free of cognitive impairment. It seems therefore that there is a difference in results between the tracers used and the accuracy of the experiments. Also a study of Yamaki, et al. (1996) showed discrepancies between tracers in the resting state.

Currently it is yet unknown which tracer is preferable. As long as there is no certainty about the tracer to be used, the glucose tracer may be preferred since there is no intern cyclotron needed in the clinical centre. Further research is needed to reveal the difference between the available tracers.

Degree of severity of TBI

A brain scan (mostly CT) is taken of almost all patients immediately after sever injury. Many moderate TBI patients, yet hardly any with mild TBI, are scanned. In time only a small part of these patients returns to medical care. As most results are obtained from patients with severe injury, it is unknown to what extent the findings are applicable to patients with mild TBI.

Time elapsed between injury and imaging

Another bias and restriction in the use of the research results is caused by the generalization of the time elapsed between injury and the functional and structural scanning of the patients. In the acute phase, usually only a structural scanning is taken whereas later on in chronic phases functional scanning is used. Apart from the bias due to the difference in elapsed time itself (acute versus chronic phase), the time difference often is correlated with different imaging methods. This can lead to a double bias.

After the primary impact of head injury, it is assumed that in the first two weeks the brain is able to regenerate functions of damaged brain tissue. These processes take place not only in the damaged brain areas or neurons; also contralateral diachisis occurs. This is in line with the tryphasic pattern of metabolic changes, as suggested by (Marvin Bergsneider, et al., 2001). Both a first brief response, hyperglyosis and a second “metabolic depression” phase, appear to have physiological consequences. These metabolic recovery with regard to CMRglc, begins approximately one month post injury.

Several previous studies suggest no predictive role for PET-imaging by TBI in the acute phase. The recovery of brain areas by changes in metabolism may be hard to predict since there is a large diversity in metabolism in the acute phase. To determine predictable value and to evaluate whether this tryphasic pattern really exists, both predetermined, repeated and simultaneously taken structural, as well as functional imaging, is therefore necessary and essential.

Age of patient

Also differences in patient characteristics have to be taken into account, especially the age of the patient. TBI is largely a younger and older person’s disorder, but the largest group exists of male persons younger than 30 years, who are in the later stages of adolescent development or early adulthood. TBI disrupts an important period of life, involving educational and social development, emerging vocational productivity and adult independence. The conclusions drawn for this group may not apply to older patients (psychological well developed) with whom TBI may manifest itself in quite different ways and symptoms.

Older people often show additional particular problems related to ageing and are more vulnerable to complications of injury and treatment. It may be difficult to distinguish these symptoms from those related to the brain injury (Zasler, et al., 2007);(Hukkelhoven, et al., 2003).

1.6 Conclusion

The aim of this review is to calculate the accuracy of PET imaging by in TBI patients. Out of an evaluation of 45 studies, 25 studies appeared to be relevant and showed that PET-imaging is significant superior to structural imaging with a sensitivity of 97% for PET-imaging, against 44% for structural imaging.

Despite this superiority in sensitivity of detecting TBI, previous studies suggest that PET-imaging has no predictive value with regard to the development of, and recovery from TBI. This suggestion may not be valid as the used studies showed a large heterogeneity in methods applied and in patient characteristics. Potentially confounding variables are the type of tracer used, time elapsed between injury and imaging, method of comparison between abnormal and normal tissue areas, degree of severity of TBI and age of the patient (recovery potential).

With respect to the way of comparison between groups of patients with TBI, Statistical Parametric Mapping (SPM) seems to be the best quantitative analysis method.
With regard to the tracer to be used further research is needed. So far there is no certainty about the best tracer to be used. For the time being the glucose tracer may be preferred since this tracer has no obvious disadvantages (yet) to other tracers but does not require an intern cyclotron in the clinical centre.

Differences in patient characteristics have to be taken into account, in particular the age of the patient. Another heterogeneity patient characteristic is the severity of the injury. As most results are obtained from patients with severe injury, it is unknown to what extend the findings are applicable to patients with mild TBI.
Apart from the bias due to differences in time elapsed between injury and imaging, the time difference often is correlated with different imaging methods. This can lead to a double bias.

A solid conclusion with regard to the predictive value of PET scanning can therefore only be drawn after standardizing the methods (tracer, the use of SPM-type references, time elapsed between injury and scanning,) and by using homogenous groups of patients, according to the severity of TBI and patient's ages,

To determine the best method for detecting abnormalities in the brain as well as (the absence of) a predictive value of PET imaging, prospective, repeated and simultaneously taken structural and functional imaging under the above mentioned conditions, need to be performed and compared.

Study 2 | A correlation of metabolism outcome and cognitive function in specific brain areas in patients with Traumatic brain injury.

2.1 Introduction

Cognitive deficits are common consequences of traumatic brain injury (TBI). These consists of complex combinations of memory, attention and executive functions disorders, slowed information processing and changes of behaviour and personality (Fontaine, et al., 1999; Zasler, et al., 2007). The relation between the damaged area and the cognitive consequences is not fully understood (Nakashima, et al., 2007).

Several studies state that structural neuroimaging sometimes fails to detect abnormalities in patients with neuropsychological and cognitive deficits, especially in Mild TBI (Chen, et al., 2003; Shiga et al., 2006 ;Mattioli et al., 1996; Fontaine, et al., 1999).

Functional imaging has the potential to reveal cerebral dysfunctions and several studies have tried to find a relation between regional cerebral dysfunction and cognitive deficits with the use of functional imaging like Single-Photon Emission Tomography (SPECT) (Ichise, et al., 1994) and Positron Emission Tomography (PET) (Fontaine, et al., 1999; Gross, et al., 1996).

Functional imaging like fluorine-18 fluordeoxyglucose PET (FDG-PET) is able to indicate changes in the cerebral glucose metabolism (Gazzaniga, Ivry, & Magnun, 2002; Zasler, et al., 2007). The interpretation of the images is based on the assumption that regional cerebral metabolism reflects the neuronal activity of the region, which implies that focal hypometabolism indicates a structure of neuronal dysfunction. FDG-PET has an advantage over SPECT as SPECT is only able to indicate the cerebral perfusion and not the metabolism; FDG-PET can indicate both.

Although few studies have used FDG-PET to explore the lesions correlated with neuropsychological deficits after TBI and showed promising results (Fontaine, et al., 1999; Gross, et al., 1996; Nakashima, et al., 2007; Ruff, et al., 1994), caution is required when interpreting these results because a large heterogeneity exists within these studies as is unveiled in section one of this study. Fontaine *et al.* (2009) for instance make no distinction in the patient characteristics and in the elapsed time between the injury and moments at which the functional imaging was taken (1-12 months).

2.2 Aim

This study is a part of a larger study and aims to find correlations between cognitive deficits and hypometabolism in different brain structures. In this study a standardized method is used in which a distinction is made with regard to the characteristics of the patients. This part of the study focuses on patients with mild TBI and had a PET scan at least one year post-injury. In this study it is assumed that when a specific brain region is damaged it results in a specific cognitive deficit. A correlation was sought between cognitive deficits as revealed by neuropsychological tests and hypo-glucose metabolism in specific brain areas, during the resting state of patients.

2.3 Methods

Patients

In this study performed in *De Winkler Kliniek* (Pro persona, Wolfheze, the Netherlands), eight patients with mild traumatic brain injury, as defined by an initial score of more than 13 on the Glasgow coma scale or posttraumatic-amnesia less than hour, were followed in their recovery. All patients are in the chronic phase of TBI (more than a year post-injury) with an average time elapsed since injury of 5.9 year (± 3.5 and a range of 1-11 years). At the moment of PET-imaging the mean age of the patients was 41.3 year (± 18.1 and a range of 19-66 year).

As shown in table 1, six patients, out of these eight, do not show abnormalities with structural imaging (MRI).

Table 1 *Characteristics of patients with brain injury*

Patient	*Sex*	*Age at injury in years*	*Time injury in years to PET*	*Severity of TBI*	*Structural imaging*
1	F	20	2	Mild	Normal
2	M	66	9	Mild	Abnormal
3	M	19	5	Mild	Normal
4	M	37	11	Mild	Normal
5	M	44	7	Mild	Normal
6	M	29	4	Mild	Normal
7	M	54	8	Mild	Normal
8	M	61	1	Mild	Abnormal
Mean ± SD		41.3±18.1	5.9±3.5		

Positron-emission Tomography

In this study the eight patients were scanned with FDG PET on an ECAT EXACT HR^{+} PET scanner (Siemens/CTI, Knoxville TN). The scanner acquires 63 contiguous transaxial planes, simultaneously covering 15.5 cm of axial field of view. Transaxial and axial resolution of the PET system were measured at 4.5 and 6 mm (FWHM at 10 cm). Data acquisition followed a standardized protocol. Each patient was examined in a fasting state with eyes open, ears plugged, and in a moderately lit environment. The head of the patient was fixed in a foam cushion and adequately positioned in the gantry. Acquisition started with a 15-minute transmission scan (^{68}Ge-sources) used for subsequent attenuation correction. After the transmission scan, 120 MBq [^{18}F]FDG were intravenously administered. A PET study was obtained from 30 to 60 minutes post-injection (3 frames, 10 minutes/frame, 128 x 128 matrix, 3D acquisition). Images were reconstructed by filtered back projection using a Hann filter with a cut-off frequency of 0.5 Nyquist and corrected for scatter and attenuation. A time activity curve of the FDG concentration in blood plasma was obtained by sampling arterialized venous blood starting immediately post injection up to 45 minutes post injection. The conversion of image voxel values from nanocuries per cubic centimeter to micromol of glucose per

100 grams of tissue per minute (µmol/100g/min) was performed using the methods described by Sokoloff [1], generating rCMRglu.

The scans were normalized in comparison with brain Regions Of Interest from a data-base of a normal control group (N=12 normals. The average age of the control group is 33.6 ± 4.8 years, ranging from 25 to 40). Sixty-three Regions Of Interest (ROIs) were obtained, independent of the clinical information. The semi-quantitaive values of each ROIs were considered to be abnormal by confidence of 95%: which means a z-score less than -1.64 from normative values of the database.

In this study the number of patients, showing specific hypometabolism rCMRglu smaller than the confidence interval of 95% (z-score <-1.64) in any given ROI, was too small for meaningful statistical evaluation (see table 2). PET ROIs were therefore combined to represent seven brain domains. These domains are 1) Frontal domain, 2) Temporal Domain, 3) Parietal domain, 4) Occipital domain, 5) Occipitemporal domain, 6) Cingulate cortex, 7) Subcortical domain. Abnormal hypometabolism (rCMRglu) was only found in the frontal domain, temporal domain and subcortical domain. The subcortical domain include the thalamus, brain stem, putamen, nucleus caudatus and the insula. The combining of domains took place according to the anatomical and biochemical anatomy of the brain areas defined by Gray's anatomy (Gray, Standring, Ellis, & Berkovitz, 2005).

Table 2 *Brain regions and Frequency of abnormal rCMRglu*

Brain Region with hypometabolism	***Asymmetry***	***Patient***
Medial frontal gyrus	Right	2
Sup. Pars. Med. Frontal gyrus	Right and Left	8
Paracentral lobule	Left	7
Rectus Gyrus	Right	2
Orbital Gyrus	Right	2, 3, 5
Inferior parietal lobule	Right and Left	8
Caudate nucleus	Right	1, 2, 5, 7, 8
Caudate nucleus	Left	1, 5, 6, 7, 8
Insula	Left	2, 7

Neuropsychological Test

The cognitive impairments of the patients were diagnosed by administering a standard battery, including malingering tasks. This was done because there is always an element of doubt about the validity if neuropsychological findings due to the subjectivity of behavioural measures. Neuropsychological assessment has been criticized because measures of cognitive functioning may be influenced by the patients' cooperation, motivation, mood fluctuation or even pre-existing cognitive limitations. This was the case with three out of the eight patients and therefore the results of neuropsychological tests are not valid for interpretation of these three patients. One patient refused to participate in neuropsychological tests. The remaining 4 patients had neuropsychological tests results on four cognitive domains: 1. verbal memory, 2. visual memory, 3. working memory 4. attention, concentration and information processing and 5. planning. The neuropsychological tests are combined

according to Lezak, et al., (2004). The verbal memory domain was obtained by combining the data of the Complex figure test. The verbal memory domain was obtained by combining the data of the 15-word task and for the working memory domain the digit span task was obtained. The attention domain was obtained by combining the subtest of the Trail Making Test (TMT), measurement speed of information processing and mental flexibility. The Planning domain was obtained by combining two subsets (Key-search task and the zoo-task) of the behavioural assessment of dysfunctional Syndrome (BADS). All four patients show cognitive impairment in at least one domain.

Data-analyses

A 2x2 chi-square analysis was conducted for each of the correlations in table 5 based on dichotomous results of NPO testing and PET results in order of abnormal (z-score < -1.64) versus no abnormalities (z-score >-1.64). A 2x3 chi-square analysis investigated the correlations between brain regions and malingering outcome.

A Spearman rank-order correlation was conducted between the normalized metabolic values and the grouped neuropsychological z-scores.

2.4 Results

Brain Regions and Frequency of abnormal hypo-rCMRglu

Table 2 presents the brain regions with decreased metabolic activity. As shown in table 2 the most affected regions are the orbital gyrus (three occurrences) and the caudate nucleus (five occurrences in both the left and the right hemisphere).

Within the seven obtained domains of brain regions abnormalities were only found in three brain areas: Frontal domain, Parietal domain and the Subcortical domain as shown in table 3.

In the other four brain areas (Temporal domain, Occipital domain, Occipitemporal domain and the Cingulate cortex) no abnormalities were found.

Table 3 *Brain regions and frequency of abnormal rCMRglu (<-1.64)*

Abnormal rCMRglu	Brain region		
	Frontal	*Parietal*	*Sub Cortical*
The total number of abnormalities	**9**	**3**	**12**
Number of the 8 patients	**5**	**2**	**6**

Neuropsychological Test findings and abnormal hypo-rCMRglu

The aim of this study is to find out whether any of the impairments of the cognitive domains, as shown in persistent neuropsychological test findings, is correlated with brain regions showing abnormal hypometabolims. Table 4 sumerizes the outcome of the chi-square analysis.

As shown in table 4, due to a lack of data, chi-square analysis finds no significanct differences between the three brain regions and the five cognitive domains. Therefore the results are interpreted as being descriptive.

With regard to the frontal domain only the results concerning the working memory are as expected. This cognitive domain is the only one that shows true abnormalities and true no abnormalities between cognitive problems and hypometabolism in the frontal brain area as show in green in table 4. area. Within the other cognitive domains there are false positives (no cognitive problems but abnormal brain activity, hypometabolism) and false negatives (cognitive problems but no abnormal brain activity, hypometabolism).
For the partial region many normalities and abnormalities are not recognized or falsely attributed with regard to the deficits in the cognitive domains.

Table 4 *Comparison of cognitive domain and brain regions*

		Brain Region						
		Frontal		Parietal		Subcortical		Total
		Normal	*Abnormal*	*Normal*	*Abnormal*	*Normal*	*Abnormal*	
Visual Memory	*Normal*	1	1	2	-	-	2	
	Abnormal	1	-	1	-	-	1	3
Verbal Memory	*Normal*	-	-	-	-	-	-	
	Abnormal	2	2	3	1	-	4	4
Work memory	*Normal*	1	-	1	-	-	1	
	Abnormal	-	2	1	1	-	2	3
Attention	*Normal*	-	1	1	-	-	1	
	Abnormal	2	1	2	1	-	3	4
Planning	*Normal*	1	1	1	1	-	2	
	Abnormal	1	-	1	-	-	1	3

Note 1 The frequency shown in green is true positve (abormanl imaging and abnormal cognitive defict) and in blue is true negative, in white it is false positive or negative
note 2 The subcortical domain include the thalamus, brain stem, putamen, nucleus caudatus and the insula.

Also for the subcortical domain no chi-square analysis could be conducted towards the cognitive domains not only as the number of patients is too low but also as all patients showed abnormalities. To conduct a correlation analysis data are needed in two directions between the variables (normal as well as abnormal). However, the verbal memory cognitive domain is interesting: all four patients with TBI show problems in verbal memory and all four patients show abnormalities in the subcortical brain regions. This suggests a correlation but as data in the normal colomn are lacking it can not be calculated.

Spearman rank correlation:
To assess a possible clinical metabolic relationship a non-parametric test of Spearman rank-order correlation coefficients are calculated between normalized metabolic values of combined brain areas and combined neuropsychological tests. As mentioned before due to the small number of data, a correlation analysis gave no applicable results.

Apart from these results, it appeared with the Spearman rank-order analysis that the used combining of brain regions into the seven larger domains is valid. These larger domains appear to have no significant correlation ($p > 0.05$) with one exception: there was a significant positive correlation

between the cingulate cortex and the occipital domain (r_s = -.0738 N= 8 p < 0.023 two tailed*).* Thus the used method of combining brain regions into larger domains for the purpose of this study does not lead to blurring and is distinctive.

Malingering and abnormal PET and abnormal hypo-rCMRglu

Out of the eight patients, four scored below their true level in neurological tests, as suggested by malingering tasks. A chi-square analysis was conducted to assess whether malingering correlates with abnormalities in different brain regions in comparison with patients who showed persistent cognitive impairments. Table 5 summarises the results of the chi-square test of patients with malingering results and no malingering results, in comparison with abnormalities in different brain regions.

Table 5 *Comparison of malingering and brain regions*

		Brain Region metabolism					
		Frontal		Parietal		Subcortical	
	Total	*Normal*	*Abnormal*	*Normal*	*Abnormal*	*Normal*	*abnormal*
No malingering	*4*	2	2	3	1	0	4*
Malingering	*4*	1	3	3	1	2	2

**p* < 0.102 two-tailed

Note 1 The subcortical domain include the thalamus, brain stem, putamen, nucleus caudatus and the insula.

As shown in table 5 only the subcortical region shows an almost significant correlation (p <0.102) between patients with no malingering neuropsychological test results and abnormalities in brain metabolism: none of the patients with no abnormal malingering results showed abnormalities in the subcortical region. In comparison only two out of four patients with abnormal malingering results.

2.5 Discussion

The aim of this study is to find correlations between cognitive deficits and hypometabolism in different brain structures with the use of PET-imaging according to a standardized method. This study is a part of a currently running larger study and only includes patients with mild traumatic brain injury who had a PET-scan at least one year post-injury.

The chief outcome is that all of the patients in the group investigated showed at least one abnormal hypo-glucose metabolism in the frontal region, the parietal region or the subcortical regions. No abnormalities were found in other regions, as the cingulate cortex.

Despite the fact that the present study made a better distinction with regard to mild TBI, the chronic phase of injury and the used method for combining brain regions into larger domains, the results are contrary to those in studies of Fontaine et al. (1999), Gross et al. (1996) and Nakashima et al. (2007) in which abnormalities of metabolism in the area of the cingulate cortex were found. In the study of Fontaine et al. (1999) correlations with different cognitive impairments even appeared to be significant. The discrepancy between the present study and the studies mentioned above may be due to the small number of patients in the present study and unavailability of neuropsychological tests.

Another issue is the low number of abnormalities. PET-imaging cannot detect white-matter abnormalities but only cortical abnormalities. The cognitive deficits with patients with TBI are often explained due to white-matter abnormalities (Zasler et al. 2007). However Fontaine et al (1999) suggest that the cognitive deficits correlating with specific brain areas are interpreted by underlying neuronal circuits. The cingulate cortex is part of an important network involved in executive aspects of attention and has connections with other brain areas like the prefrontal, parietal and temporal cortices. Dysfunction (hypometabolism) in this area could explain why patients with TBI fail in so many cognitive domains, such as memory, attention and executive function.
In this study no abnormalities were found in the cingulate cortex, but the abnormalities were found in subcortical areas, for instance the thalamus and nucleus caudate. These areas also play an important role in neuronal circuits of attention and memory. Additionally it should be mentioned that in this study six out of eight patients show no MRI abnormalities, contrarily MRI does detect white-matter abnormalities.

Out of eight patients four did not perform well on the neuropsychological test of malingering.
This results in insufficient data in detecting a correlation between cognitive impairments and abnormal hypometabolism in brain regions. The study of Stulemeijer et al (2007) shows that the underperformance in neuropsychological test has be found earlier; 27% of the patients with MTBI failed the malingering test. The poor effort was strongly associated with low performance in neuropsychological tests. Stulemeijer et al (2007) implies that effort (malingering) testing should be part of neuropsychological assessments. The study of Stulemeijer et al (2007) as well as this study

show that it is not only essential to conduct the malingering test in clinical settings but also in experimental settings.

Stulemeijer et al (2007) also suggests that behavioural factors like distress and personality should be considered as potential threats to the validity of neuropsychological testing after MTBI. This implies that when a patient underperforms and has a normal structural and functional imaging, it is most likely that the complaints are not due to the psychopathology following traumatic brain injury.

For further research it might be interesting to study whether patients with malingering test results show fewer abnormalities in hypo-glucose metabolism compare to patients with no underperformance test results. It might also be interesting to study whether a significant difference can be found between activity in different brain areas in patients who underperformed and in patients who did not. This can be done by setting the confidence interval at 90%; it should be a one-tail analysis.

Further research with a larger group of patients is necessary to investigate whether the findings and recommendations are correct.

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Appendix 1

Cerebral imaging methods

Computerized Tomography (CT)

CT was the first imaging method to create three-dimensional images of the morphology of the body, including the brain. The principle of the CT is that the density of biological material varies and that tissue density is correlated with the absorption of x-ray radiation. High-density material such as bone, will absorb a large part of radiation resulting in light coloured images. Low density material like blood and air will absorb little radiation and give dark coloured patterns. Absorption of radiation by neural tissue lies between these extremes. The spatial resolution of CT is about 5 mm^3 to $10mm^3$ (Gazzaniga, et al., 2002).

After stabilization of the patient following an accident, a CT-scan of the head is the first step to assess the need for immediate neurosurgical intervention. Computed tomography has several advantages in obtaining an acute TBI setting, as it is a fast technique, there is hardly a risk for contraindications and it has a high sensitivity and specificity for several types of injury that are suspected in traumatic head injuries, including skull fractures, brain herniation, and intracranial bleeding. CT scans can demonstrate progression in time, size and in number of contusions as well as the amount of haemorrhage in the contusions. Despite its power in speed and sensitivity for fracture and bleed detection, CT is limited in predicting the long-term neuropsychological and behavioural outcomes of such injuries (Dubroff & Newberg, 2008; Le & Gean, 2009; Metting, et al., 2007).

Magnetic Resonance Imaging (MRI)

In contrast to x-rays used for CT, the MRI is based on the magnetic properties of organic tissue. Depending on the amount of protons and neutrons in their nuclei, atoms are sensitive for magnetic forces, like hydrogen. The protons that form the nucleus of the hydrogen atom are in constant motion, and spinning about their principal axis. This motion creates a tiny magnetic field. The normal state or orientations of these protons are randomly distributed. The MRI-scanner creates a strong magnetic field (from 1.5 up to 7 Tesla) and the magnet hydrogen protons in the brain are aligned with the magnetic field. Waves of radiofrequencies are then passed through the magnetized regions, and when protons absorb the energy of these waves, their orientation is perturbed in a predictable direction. When the radio waves are turned off, the absorbed energy is dissipated and the protons are rebounded to their random orientation. This rebound produces energy signals that are picked up by surrounding detectors. By systematically three-dimensional measuring of these signals the MRI constructs an actual image, that reflects the distribution of the protons and other magnetic agents in the tissue.

The spatial resolution of MRI depends on the strength of the magnet, but can be smaller than $1mm^3$ (with the use of the 7 Tesla magnetic field of the MRI scanner) (Gazzaniga, et al., 2002).

MRI is hardly used for imaging in the acute phases of suspected TBI because: it is difficult to diagnose skull fractures; it has limitations with getting critically ill patients into a MRI; it has a risk when metal parts are present in the body of the patient (dangerous responses to the magnetic fields) and is time-consuming in image acquisition and interpretation of it. MRI is more often used in subacute phases of

head-injury and during follow-ups. MRI is superior over CT in spatial resolution and sensitivity of detecting cerebral pathology, especially in cases of diffuse axonal injury, non-haemorrhagic contusions, small subdural haematomas, brainstem-injury and focal atrophy in the frontal and temporal regions in the chronic phase (Metting, et al., 2007).

Single Photon Emission Computerized Tomography (SPECT)

SPECT is a functional imaging technique that is used to measure heamodynamics in the brain, mainly in the sub acute phase of injury.

SPECT provides an indirect indicator of brain perfusion by measuring cerebral blood flow. A radioactive tracer is inhaled or injected into the bloodstream and spread along with the blood flow. As with PET (see below), these tracers emit gamma rays. A rotating camera detects these rays and creates several two-dimensional pictures. These pictures are combined to obtain a three-dimensional image. SPECT has a resolution of 7 mm^3. Several radiotracers are available, with 99mTc-hexamethylpropylenamineoxide (HMPO) being the most common.

Positron Emission Tomography (PET)

Also PET is a functional imaging technique. Like SPECT, to acquire a PET image, a tracer must be introduced in to the bloodstream. The tracers used are unstable radioactive elements or isotopes that break down within a few minutes. This break down occurs when a positron emits the atom of the tracer. When a positron collides with an electron of the tracer, two photons or gamma rays are created. These two photons move at the speed of light, pass unimpeded through all tissues but move in opposite directions from each other. The PET-scanner, a gamma ray detector, can determine where the collision took place. Because the tracers are introduced in the blood, a reconstructed image can show the distribution of blood flow: where there is more blood flow, there will be more radiation. By this, PET is able to describe various features of brain heamodynamic. The most frequently used tracer for detecting regional glucose metabolism is fluorine-18 labelled fluorodeoxyglusose (FDG).. Besides glucose metabolism other tracers like oxygen-15 labelled H_2O, CO and O_2, provide information of cerebral blood flow, cerebral blood volume, oxygen extraction fraction and cerebral metabolic rate of oxygen in patients with brain injury. Although quantitative data can be obtained with PET and PET offers a better resolution than SPECT, the application of this technique is limited by radiation exposure and difficult availability due to the high costs. PET is especially used as a research tool in a non-emergency setting (Bazarian, et al., 2006; Belanger, et al., 2007; Dubroff & Newberg, 2008; Gazzaniga, et al., 2002).

Functional Magnetic Resonance Imaging (fMRI)

Functional MRI is a widely used neuroimaging technique for measuring brain functioning. The idea principle is the blood-oxygen-level-depend (BOLD). It means that an increase in brain activity leads to an increase in blood flow and oxygenation of the haemoglobin molecule by the red blood cell (Belanger, et al., 2007). So when a brain region requires more oxygen because it is metabolic active, local red blood cells become deoxygenated. Deoxygenated hemoglobin, unlike oxygenated

haemoglobin, has a magnetic dipole. If enough molecules become deoxygenated within a brain region less magnetic homogeneity can be detected with the use of statistical analysis with the very homogenous magnetic field of MRI scanner.

The resolution depends on the strength of the magnetic field of the MRI scanner (3 Tesla is more sensitive than 1.5 Tesla scanner) (Dubroff & Newberg, 2008). The spatial resolution of a 7 Tesla machine is about 1 mm^3. Besides this high spatial resolution, it is free of radiation and it is possible to repeat measurements. However, the patient must be highly cooperative for the scan and needs to lie motionless in a small and noisy tube, which limits its utility in many clinical situations. As for MRI, the strong magnetic field excludes the use of fMRI for patients with metal medical aids or implants. It is promising for activating studies, but more expensive than PET-imaging.