Functional Neuroimaging in Whiplash Injury

New Approaches

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Third Edition

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"*In bunten Bildern wenig Klarheit,*
Viel Irrtum und ein Fünkchen Wahrheit …".

Johann Wolfgang von Goethe (1749–1832), *Faust I.*[1]

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[1] "*In motley pictures little clarity, much error and a spark of verity …*" (Goethe)

Preface

Whiplash injuries are often looked upon as accidents causing extensive symptomatology without the presence of objective findings. They can cause a disease condition, which is frequently denied, but is unfortunate and may become chronic and invalidating for the patient.

In the past three decades, much has been published on whiplash injury, yet both the confusion regarding the condition and the medicolegal discussion surrounding it has increased.

In this scenario, a guide on recent and current international research in the field is even more than necessary. Especially functional imaging methods—such as single-photon emission tomography (SPET) or positron emission tomography (PET)—have shown various and sometimes differing brain alterations, which should be discussed in the conflicting arena of whiplash victims, treating physicians, insurance companies, and reviewers.

This book, now in its third, completely revised and updated edition,[1] accordingly offers a critical approach to the challenging interpretation of the latest research data obtained using functional neuroimaging in whiplash injury. It covers all aspects, including the imaging tools themselves and the different methods of image analysis. Details on historical whiplash experiments and crash tests, and on biomechanics, including the finite element method, are now added. *Functional Neuroimaging in Whiplash Injury: New Approaches* will continue to help patients, their relatives and friends, involved physicians, and others to understand this condition as a disease.

Offenburg, Germany — Andreas Otte

[1] The initial idea for this book was in 2001. It was first published in German by Springerverlag under the title "Das Halswirbelsäulen-Schleudertrauma: Ein Ratgeber für Ärzte und Betroffene". The first English edition was published in 2012 under the title "Whiplash Injury – New Approaches of Functional Neuroimaging." This first English version already differed significantly from the original German version in that it incorporated completely new research findings and focused more on nuclear medicine imaging.

Acknowledgments

We are very happy that this book is continuously published by one of the premier publishers in the field. This guarantees a high quality of production and allows for the inclusion of many color figures, which is an essential detail in the field of functional neuroimaging.

I would like to thank Mrs. Corinna Hauser from Springer for her help and input during the development of this book.

Contents

About the Author

Andreas Otte MD, is a board-certified specialist in Nuclear Medicine and Professor of Biomedical Engineering in the Division of Medical Engineering, Department of Electrical Engineering, Medical Engineering and Computer Science, Offenburg University, Germany. Prof. Otte received his graduate and postgraduate medical education at the University Hospitals Freiburg, Germany, and Basle, Switzerland, and at the Paul Scherrer Research Institute in Villigen, Switzerland. Thereafter he held various leading positions in clinical research with Pfizer in Freiburg, Germany (International Medical Research, Pfizer Global Pharmaceuticals) and at the University Hospital Freiburg.

From 2002 to 2009, he was a Visiting Professor of Nuclear Medicine in the Medical Faculty of the University of Ghent in Belgium. He took up his present position in 2010.

Andreas Otte is the author of many peer-reviewed journal articles and the author or editor/coeditor of a number of books, including the Springer trilogy *PET and SPECT in Neurology, PET and SPECT in Psychiatry,* and *PET and SPECT of Neurobiological Systems*. His research focus is on neurosciences including functional neuroimaging, brain-machine interfaces, and intelligent neuroprosthetics. He is member of the Offenburg University research institutes *Campus Research & Transfer* and the *Peter Osypka Institute of Medical Engineering*.

Awarded a series of international scientific prizes, he was nominated Editor of the Board of the *European Journal of Nuclear Medicine* (1998–2003), the *Hellenic Journal of Nuclear Medicine* (since 2003), *Archiv für Kriminologie [Archives of Criminology]* (since 2020), and *Prosthesis* (since 2020).

Abbreviations

^{11}C	Radioactive carbon-11 positron emitter
^{15}O	Radioactive oxygen-15, positron emitter
^{18}F	Radioactive fluorine-18, positron emitter
^{57}Co	Radioactive cobalt-57, gamma emitter
^{99m}Tc	Radioactive technetium-99m, gamma emitter
AC-PC line	Line between anterior and posterior commissure of the brain
AI	Artificial intelligence
CT	Computer(ized) tomography
DTI	Diffusion tensor imaging
DTT	Diffusion tensor tractography
ECD	^{99m}Tc-ECD (ethylene biyldicysteinate dimer, Neurolite™), perfusion marker used in SPET
EEG	Electroencephalography
EMG	Electromyography
FDG	Fluorodeoxy-D-glucose, glucose analogon; labeled with the positron emitter fluorine-18, it is used in PET as glucose metabolism marker
FEM	Finite element method
fMRI	Functional magnetic resonance imaging
g	Acceleration constant of the earth
GMI	Glucose metabolic index
HMPAO	^{99m}Tc-HMPAO (hexamethyl propylene amine oxime, Ceretec™), perfusion marker used in SPET
i.v.	Intravenous(ly)
lat.	Latin
Lb	Lat. libra: pound
MEG	Magnetoencephalography
mph	Miles per hour, also m.p.h.; 1 mph = 0.44704 m/s = 1.609344 km/h
MR/PET	Combination of magnetic resonance imaging and positron emission tomography in a hybrid scanner system
MRI	Magnetic resonance imaging
ms	Millisecond
NIRS	Near-infrared spectroscopy
NK1	(Substance P) neurokinin-1, receptor
PET	Positron emission tomography

PET/CT	Combination of positron emission tomography and computer tomography in a hybrid scanner system
PI	Perfusion index
q.i.d.	Lat. quater in die: four times a day
rCBF	Regional cerebral blood flow
ROI	Region of interest
SPET	Single-photon emission tomography
SPET/CT	Combination of single-photon emission tomography and computer tomography in a hybrid scanner system
SPM	Statistical Parametric Mapping
SQUID	Superconducting quantum interference device
T	Tesla
t	time
t.i.d.	Lat. ter in die: three times a day
TAI	Traumatic axonal injury
Δv	Change of speed, v velocity

Introduction

1

Arma virumque cano, Troiae qui primus ab oris
Italiam fato profugus Lavinaque venit
litora – multum ille et terris iactatus et alto
vi superum, saevae memorem Iunonis ob iram,
multa quoque et bello passus, dum conderet urbem
inferretque deos Latio – genus unde Latinum
Albanique patres atque alta moenia Romae.
("I sing of arms and the man, who—exiled by fate—first came from the Trojan coasts to Italy and the Lavine shores; was much smitten on land and sea by violence from Heaven, through cruel Juno's unforgiving wrath, and suffered much in war, until he could found the city and bring over his gods to Latium, from where arose the Latin race, the fathers of Alba and the high walls of Rome.")

Publius Vergilius Maro (70–19 B.C.), Aeneïs

1.1 General Aspects

Whiplash injury (with a distortion of the cervical spine) and its consequence (the late whiplash syndrome) are continuously controversial medicolegal challenges. The ongoing ambiguity with the presence and extent of the late whiplash syndrome leads to multiple disconcertion not only in the accident victims but also in treating physicians, attorneys, judges, or insurance companies. The late whiplash syndrome has become one of the most unresolved odysseys of modern times for many patients (therefore our quotation from Vergil's *Aeneïs* at the beginning of this chapter, since the Aeneid by Vergil is based on the Iliad and Odyssey attributed to Homer, describing the flight of the mythological Aeneas from burning Troy and his odysseys that finally lead him to Latium).

A. Otte, *Functional Neuroimaging in Whiplash Injury*,
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1.1.1 The Term "Whiplash Injury"

By definition, no head impact may be associated with a whiplash injury. Since the introduction of head restraints into the modern automobile, this, however, in most cases does not apply anymore. Collision forces, which do not have to necessarily leave traces, can lead to the so-called closed head injuries. Even with a pure acceleration mechanism without head impact, it can come to direct cerebral injuries (Fig. 1.1), as *Ommaya and coworkers* could show already in 1968 in a monkey experiment (Ommaya et al. 1968):

- In Ommaya's project, more than 50 rhesus monkeys were anesthetized with barbiturate and placed in a special chair that was mounted on a rigid carriage equipped

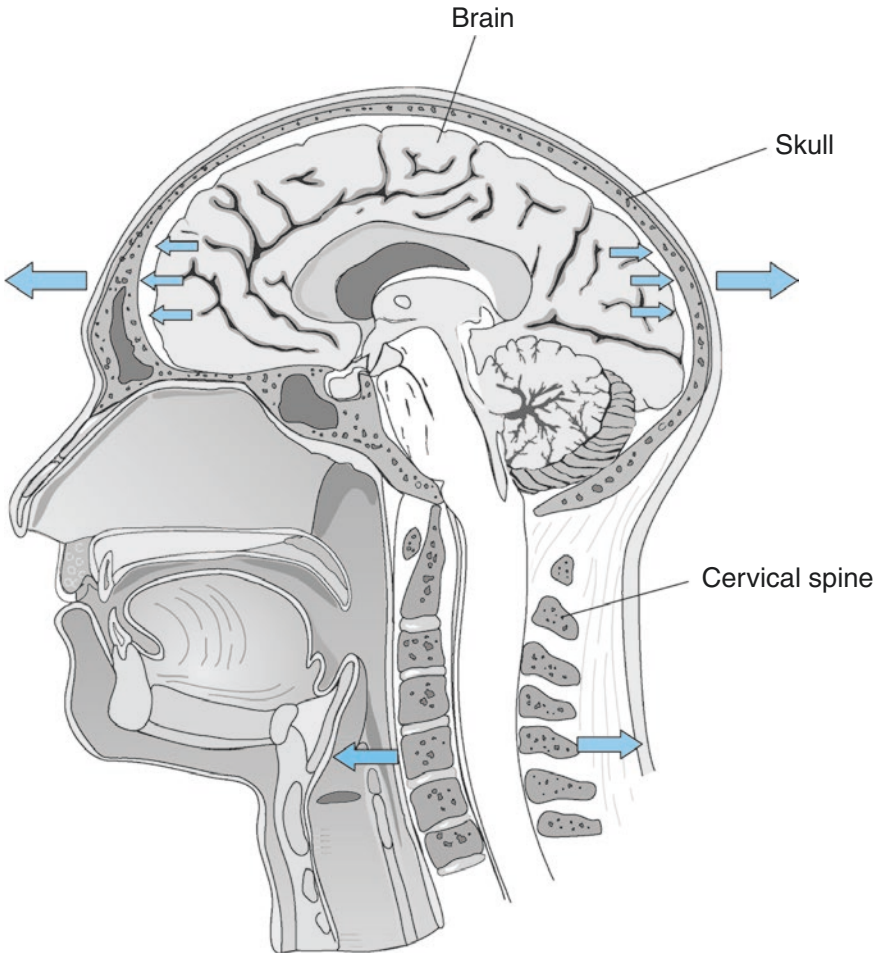

Fig. 1.1 "Whip–lash" injury: In whiplash injury, apart from the cervical spine, also the head, which is embodied at it, moves. In the head, the brain can be likewise pulled by impact on the bone wall. (Adapted from Otte et al. (eds) (2004) Nuclear Medicine in Psychiatry, Springer, Heidelberg)

with roller-skate wheels and moved over a 12 feet long track. A pressure chamber ("impacting piston") produced high acceleration forces ("blows") to the carriage, and a braking system achieved gradual deceleration of the carriage mimicking a rear-end collision. The whole procedure was called the "whiplash injury apparatus." The resulting whiplash mechanism of the head on the neck and shoulders was recorded by a high-speed cinematographic camera at 1000 frames/s allowing for measurement of the rotational or angular displacement of the head and thus calculation of the rotational velocity and acceleration. Afterwards the brain and proximal spinal cord were removed by autopsy. Depending on the level of acceleration, the brain was concussed or not concussed. 19 monkeys had concussions of the brain, 15 of these 19 primarily had subdural hemorrhages. In the 22 non-concussive monkeys none had any macroscopic evidence of brain damage or any surface hemorrhages. Although Ommaya does not further investigate the non-concussive brains, these pioneering experiments, as we think, are pivotal for investigating potential brain damage following whiplash injury for the first time in history.

Even in 1969, *Ommaya* describes two impressive clinical whiplash injury cases in humans, which read as follows (Ommaya and Yarnell 1969):

> FIRST CASE: On Oct. 1, 1965, a 62-year-old male physician was sitting in his car waiting for a traffic light to change. His lap seat belt was securely buckled. Without warning a 10,000 lb fully loaded truck ran into the back of his car at about 30 m.p.h. He could recall the sudden rotation of his head backwards to the left, without striking any object forcefully. The lap belt limited the initial forward motion of his body and his head did not strike any part of the car. He got out of his car immediately, but he found himself uneasy if standing and sat down during the 20-minute police interrogation. He then drove to his place of work, the New York University Hospital. On arrival, he was examined by an internist and an orthopedic surgeon because of considerable pain in the neck and along the medial border of the left arm. Pressure on the left side of c7 and T1 spinous processes caused stabbing radicular pain along the medial border of the left arm. He had no complaints referable to the head or upper-motor neurons, and X-ray of the cervical spine revealed no abnormality. By the following day the neck pain had increased, but over the next days the pain gradually subsided and he resumed normal work. On the tenth day, he noticed generalized headaches, progressive lethargy, and dulling of mental function. Within 3 weeks, these symptoms were quite severe and he required large doses of analgesic for his headaches. At about this time he also noted increasing weakness in the right leg and within the next 48–72 hours this had progressed to the right arm. He thought he was having a stroke and was promptly admitted to hospital. On admission, his past history was found to be significant only for one anteroseptal myocardial infarction in 1960 from which he had recovered without sequelae. He had been on pentacrythritol tetranitrate 20 mg. q.i.d., but this was taken very irregularly along with meprobamate 400 mg. at bedtime. Examination revealed a right hemiparesis, worse in the leg, no papilloedema, or visual field deficit. Blood-pressure 110/72 mm Hg; pulse-rate 60; other laboratory findings normal. Electrocardiography revealed low R waves in V1–V6 (previous anteroseptal infarct). Skull X-ray showed dorsum sella intact, pineal not calcified, no evidence of raised intracranial pressure. Cerebrospinal fluid clear and colorless, 4 red and no white blood-cells, protein 38 mg. per 100 ml. Echo-encephalogram, 3 mm. shift from left to right (normal 2 mm.) A slowly evolving cerebrovascular thrombosis was diagnosed. The next day the right hemiparesis had increased and mentation was slow. A course of i.v. heparin was instituted, and over the next 24 hours he was given 225 mg. The clotting-time on this regimen remained just below 22 minutes as compared to the initial clotting-time of 6 minutes (Lee White). The next day however, he was worse and the right-sided deficit had become both motor and sensory. A left-carotid angiogram revealed a 2 cm. thick, middle, and high parietal

subdural hematoma. This was evacuated via a left parietal craniotomy. The outer membrane was completely removed as a grayish-tan sheet. The contents were entirely liquid and the inner membrane was only partly removed. The brain immediately reexpanded to fill about 50% of the intracranial cavity above the hematoma. The patient was started on phenytoin ('Dilantin') 100 mg. t.i.d. and soon recovered. By discharge on the tenth postoperative day, the strength of his right limbs had almost completely returned. He returned to work 5 months after the operation. Two attempts at stopping his dilantin led to recurrence of clumsiness and paresthesia in the right arm, so dilantin 100 mg. t.i.d. was continued. 3 1/2 years after the accident he is working fulltime with no residual sensorimotor or intellectual deficits.

SECOND CASE: This middle-aged woman was driving her car at an unknown speed when she ran into an immovable barrier. She was thrown forcibly forward, her head flexing on her chest and then moving backwards. She was restrained by a lap belt, and claimed that she did not strike her head against any part of the car interior. 5 days after the accident an orthopedic surgeon found painful limitation of neck motion and localized tenderness in the back of her neck. Her complaints at this time consisted of occipital headaches, neck pain, and mild vertigo. Cerebral concussion plus cervical sprain was diagnosed. By the next day, however, she complained of increasing discomfort and nausea. On the seventh day after the accident she became very weak and drowsy and was re-examined. An almost complete left hemiplegia was noted. No special investigations were done, and she was kept in for observation. 8 days after the whiplash injury the patient had become much more unresponsive and her pupils were unequal. Preparations for brain scan and cerebral angiography were under way when she suddenly died. Necropsy revealed a large subdural hematoma compatible with the neurological deficits which had developed in her clinical course.

1.1.2 Symptoms

In all stages of a whiplash injury by acceleration forces, in addition to peripheral symptoms such as neck pain and neck rigidity,[1] it can come to central, i.e., cerebral, symptoms. According to the *Quebec Task Force on Whiplash Associated Disorders* (Spitzer et al. 1995), these cerebral symptoms comprise headache, dizziness, vertigo, tinnitus, concentration, attention and memory disturbances, and temporomandibular dysfunction. Furthermore, often visual symptoms such as blurred vision or oscillopsia are reported.

Both the peripheral and the central symptoms arise typically with a characteristic latency of 0–72 h. Especially, the cerebral symptoms are of utmost relevance for the development of chronic stages and often subject to the various controversial discussions on the causality of the disease. The frequent absence of objective findings in the late whiplash syndrome increases this problem.

In this situation, methods are welcome, which can capture the objective condition of the brain. Due to the controversial discussion of the topic, such methods are, however, often rejected.

[1] The cervical spine is a statically complicated structure in which muscles and ligaments attempt to build up axial pressure in all postures. In flexion and extension positions, the load that can be absorbed by the cervical spine is reduced and amounts to 500 kg in flexion and 100 kg in extension without damaging the intervertebral disc (Gareiss et al. 2020). In our book, however, we would like to focus on the skull and the brain and refer to other relevant literature on the cervical spine and its changes after a whiplash injury.

1.2 Incidence

Whiplash injuries may occur anywhere: in traffic accidents, accidents at sports, or at work. They are not necessarily limited to car accidents with a rear-end collision mechanism, although rear-end car collisions represent the most frequent cause for whiplash trauma. Crucial is only the accident mechanism, i.e., the presence of a cervical distortion with or without cerebral participation (Fig. 1.2).

According to the *Quebec Task Force on Whiplash Associated Disorders* (Spitzer et al. 1995), only about 5% of the whiplash-injured develop a chronic disease beyond 1 year after the accident, while the other part recovers from initial symptoms within a few weeks after the accident. By contrast, Carroll et al. (2008) report a much worse outcome with up to 50% of patients developing persistent symptoms.

Also, more women than men suffer from whiplash trauma (ratio 1.5–1) (Quinlan et al. 2004), and women more frequently develop long-term symptoms (odds ratio: 1.54) (Walton et al. 2009).

According to Schmid (1999), the incidence of whiplash injuries in the industrialized countries is up to 3.8 cases per 1000 inhabitants per year. Evans (1992) reported of more than one million cases per year in the USA. Holm et al. (2008) report 300 of 100,000 people per year in North America and Western European countries suffering from symptoms after a whiplash injury.

Within the European Union, the subsequent annual costs are estimated at least €10 billion (Report 2005) and $29 billion in the USA (Freeman et al. 1999). The largest portion of these costs comprises substitution of the failing regular income.

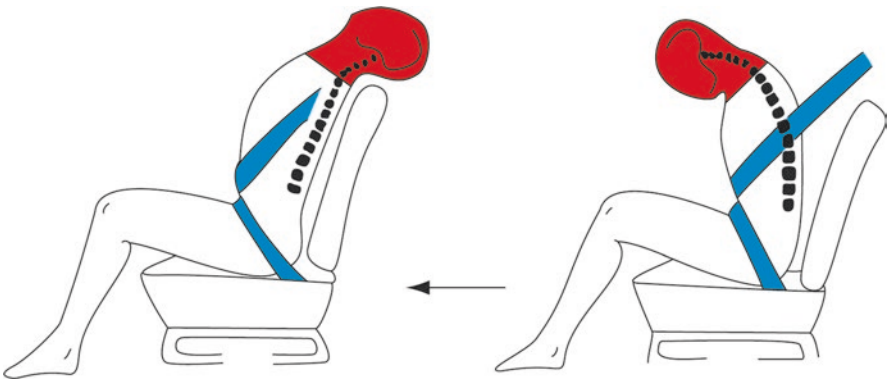

Fig. 1.2 Scheme of a typical whiplash mechanism, e.g., following a rear-end car collision. During sudden acceleration of the fixed trunk, the unfixed head is accelerated first to the rear and then forward. Already low speeds between 10 and 20 km/h can cause large acceleration forces on the head (Croft 1998; Olsson et al. 1990; Ryan et al. 1993). (Adapted from Otte et al. (eds) (2004) Nuclear Medicine in Psychiatry, Springer, Heidelberg)

1.3 Historical Aspects

Central nervous system (CNS) symptoms in cervical spine alterations are not new.

1.3.1 Barré's "Syndrome Sympathique Cervical Postérieur"

Already in 1926, the French neurologist Jean Alexandre Barré (1880–1967) described a characteristic complex of symptoms in patients with cervical diseases, which, in part, is known from the late whiplash syndrome (Barré 1926; Pearce 2004):

> Les symptôms craniens consistent surtout en:
>
> 1. Céphalées, à maximum occipital,
> 2. Des troubles vertigineux qui surviennent à chaque instant quand le malade tourne la tête, et qui ne s'accompagnent ordinairement pas de modifications nettes des épreuves vestibulaires instrumentales,
> 3. Des bourdonnements d'oreilles,
> 4. Des troubles visuels qui empêchent les malades de lire longtemps, leur font croire que leur vue a baissé; ces troubles les conduisent souvent chez l'oculiste, qui ne constate généralement aucune modification objective de la vision, parce qu'il fait l'examen chez le malade au repos et que la fatigue seule est propre à faire apparaître le trouble.[2]

1.3.2 The Term "Railway Spine"

In the nineteenth century, the (British) term "railway spine" was established in a time when traveling by train became popular (Harrington 1996; Keller 1995; Caplan 1995; Fischer-Homberger 1970; Otte 2001a, b). It was assigned to patients with posttraumatic symptoms and no apparent lesions after train accidents, and it was hypothesized that these symptoms were related to molecular spinal damage. Although the medicolegal discussion became obsolete after 1900 as a consequence of an increasing number of malingerers and fraud, the controversy on the phenomenon "railway spine" may have been a precursor for some of the discussion on posttraumatic symptoms today.

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[2] "The cranial symptoms mainly consist of:

1. Headache, preponderantly occipitally;
2. Vertiginous disturbances, which occur every moment when the patient turns his or her head, and which normally are not accompanied by any clear modification of instrumental vestibular tests;
3. Tinnitus;
4. Visual disturbances, which prevent the patients from reading a long time, make them believe that their sight has fallen; these disorders often lead them to the oculist, who does not generally observe any objective change in vision, because he examines the patient at rest, but only fatigue can show the disorder." (Barré 1926).

1.3.3 The Case of Maurice Ravel

The famous French composer Maurice Ravel (1875–1937) enriched the music with fantasy and new ideas like no other. Main impressionistic works are *Jeux deau* (1901), the string quartet in F major (1902–03), the *Sonatina* (1903–05), the cycles *Miroirs* (1904–1905) and *Gaspard de la nuit* (1908), the *Rhapsodie espagnole* (1907–1908), *Lheure espagnole* (1911), the post-Schubertian *Valses nobles et sentimentales* (1911, orchestrated 1912), and the languorous ballet *Daphnis et Chloé* (1909–12), which is in the vision of ancient Greece through modification of eighteenth century French classicism. More and more, Ravels music turns to the aesthetic classicism in the following years, to mention the piano trio (1914), the suite *Le tombeau de Couperin* (1917, orchestrated 1919), which is full of old French music and predates Stravinsky's neoclassicism, then the first post-war piece *La valse* (1920), where the three-fourth rhythm develops into a dance macabre, *Tzigane* (1924), and the sophisticated fantasy opera *Lenfant et les sortilèges* (1925), with the delights and dangers of a child's world.

The most famous work of Ravel is without doubt the ballet *Boléro* (1928). The first performance of the *Boléro* was 1928 at the Paris Opera. The stage set was an Andalusian tavern; Ida Rubenstein danced the *Boléro* on a table, at first with slow, gliding movements, then with increasing passion until the gypsies began to dance with her. The scene ended in a wild whirl of dancers who at the end crowded more and more closely together and drew their knives. From a compositional point of view, the *Boléro* was primarily intended as an orchestration study; a rhythmical ostinato and two ostinato melodies, which are in total repeated 18 times, cumulate with an always increasing number of instruments into a turbulent fortissimo. The almost ritual effect of the *Boléro* is achieved by renunciation: Ravel did without elaborated motives and without a fancy musical form or modulations. Only at the very end an abrupt change can be heard from C major to E major. In fact, the *Boléro* is reported to be the world's most frequently played piece of classical music.

The two piano concertos are both composed in 1929–1930. The concerto in G major for both hands is "delightful and brilliant …, in the spirit of Mozart and Saint-Saëns" (Ravel 2018), whereas the concerto in D major for the left hand, which is in one movement only, is composed in an impressing new pianistic and symphonic style showing many effects derived from jazz music. Ravel was interested in jazz concerts since the early 1920s and, in fact, in close contact with George Gershwin (1928 in New York), which may have influenced this piece; the work was commissioned by the Austrian pianist Paul Wittgenstein, who lost his right hand during World War I.

In October 1932, Ravel was injured in a car accident while sitting in a taxi in Paris. As a consequence of this accident, a head injury was reported; Ravel also lost a few teeth and had a short mild concussion. It is reported that he was treated by "needles" (acupuncture) and hypnosis (Otte et al. 2003a, b; Otte and Wink 2008). From the day of this accident on, after having written down his last composition, the cycle of songs *Don Quichotte à Dulcinée*, Ravel was not able to complete any composition anymore; although he tried hard to write down sketches of various new compositions he still had in his mind, he could not bring to paper any complete musical piece (Table 1.1). After 1932, Ravel, who had become an international celebrity,

Table 1.1 Comparison of Ravel's major compositions with his major life events. After the taxi accident in 1932, Ravel was not able to write down any new composition, although his head was "full of ideas," as Ravel always tried to state

Compositions		Events
	1875	Birth
	1889	Music student at the Conservatoire of Music in Paris (1889–1905)
Habanera	1895	
Shéhérazade	1898	
Pavane pour Une infante défunte (piano)	1899	
Jeux d'eaux	1901	
3 Shéhérazade songs	1903	
Miroirs	1905	
Histoires naturelles	1906	
Rhapsodie espagnole; Gaspard de la nuit	1908	Death of father
Pavane pour Une infante défunte (orchestra)	1910	
L'heure espagnole; Valses nobles et sentimentales	1911	
Ballet Daphnis et Chloé	1912	
Piano trio	1914	
Tombeau de Couperin (piano)	1917	Death of mother
Tombeau de Couperin (orchestra)	1919	Health cure in Mégève (fever, pulse alterations, insomnia, senile involution)
La Valse	1920	
	1921	Purchase of his country house (*Le Belvédère*) in Montfort-l'Amaury near Paris
Mussorgskij: Tableaux d'une exposition (orchestration)	1922	
Tzigane	1924	
Opera "L'enfant et les sortilèges"	1925	
Chansons madécasses	1926	
	1927	Difficulties in playing the piano, dysphasia, beginning apraxia
Boléro	1928	*Doctor honoris causa* (Oxford University)
2 piano concertos	1929	
(D major for the left hand; G major for both hands)	1930	
3 chansons Don Quichotte à Dulcinée	1932	Taxi accident; aphasia, agraphia, apraxia, and severe deficits in concentration and attention
	1934	Successless health cure at Lake of Geneva
	1935	Travel to Morocco
	1937	Neurosurgery and coma (17-Dec or 19-Dec)
		Death (28-Dec)

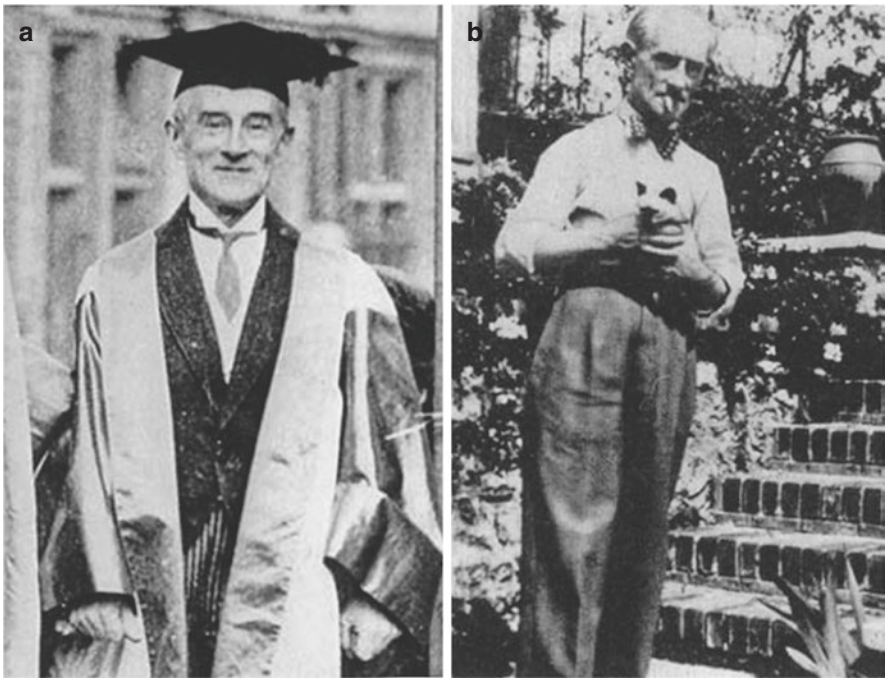

Fig. 1.3 Photographs of Maurice Ravel. (**a**) Ravel at Oxford, 1928, where he received the laureate of *doctor honoris causa*. (**b**) Ravel in his last years

was seen only rarely in public. The usual interpretation of Ravel's symptoms during his disease is frontotemporal dementia (Pick's disease) with primary progressive aphasia (Otte et al. 2003b). Linked to the taxi accident in 1932, Ravel, however, developed additional deficits in concentration and attention. Also his appearance deteriorated dramatically after this accident within only a few years (senile involution) (Fig. 1.3a, b). The question of whether Maurice Ravel had a distortion of the cervical spine resulting from acceleration forces and a consecutive late whiplash syndrome or a mild-to-moderate traumatic brain injury, of course, cannot be answered today. These diseases were not even known or defined at that time. Besides, functional imaging modalities were not available, and X-ray modalities, although discovered already in 1895 by Wilhelm Conrad Röntgen (Otte 2020), were still at the beginning of their development and some years away from the development of the first computerized tomography (CT) scanner by Godfrey Hounsfield and Allan McLeod Cormack, which first was commercially available from the British company Electric and Musical Industries (EMI) in 1972 and for which both researchers were jointly awarded the 1979 Nobel Prize in Physiology and Medicine (Otte 2016). And pneumencephalography, a radiological procedure that was introduced in 1919 by the American neurosurgeon Walter Dandy, was not carried out for Ravel.

As Ravel's health continued to worsen after the accident, Ravel's friends consulted the renowned Parisian brain surgeon Prof. Clovis Vincent, who immediately

operated the patient at his clinic in Rue Boileau on the basis of a suspected diagnosis of "hydrocephaly." Ravel died only a few days after this brain operation on December 28, 1937, only 62 years old. An autopsy was not performed.

Nevertheless, there seem to be interesting parallels between the symptoms subsequent to Ravel's taxi accident and the symptoms after whiplash injury, and we could draw this hypothetical conclusion in Ravel's case, even more as this historical case is legally unbiased today.

Recently, we have attempted to reconstruct the mechanism of Ravel's taxi accident (Otte 2021) in more detail, suggesting that it must have been a collision between the taxi, in which Maurice Ravel was sitting, and another vehicle at a relatively low speed. We do not know if Ravel was sitting behind the driver's seat, the passenger seat, or in the middle of the back seat. However, it is unlikely that he was sitting in the middle, provided that in the driver's compartment there were two spaced seats with a gap in the middle and no common front bench; otherwise some of his teeth would not have been knocked out. The loss of some teeth could be well explained by the fact that the cars of the time had relatively little padding on the back of the front seat, lacked a head restraint, and Ravel was small and slender in stature, with an unusually large head, which probably caused him to hit his mouth rather than his chin. Whether it was a rear-end car collision or a head-on collision could not be distinguished. However, in both cases the missing head restraint would trigger a pure whiplash mechanism in addition to a concussion of the brain (Fig. 1.4).

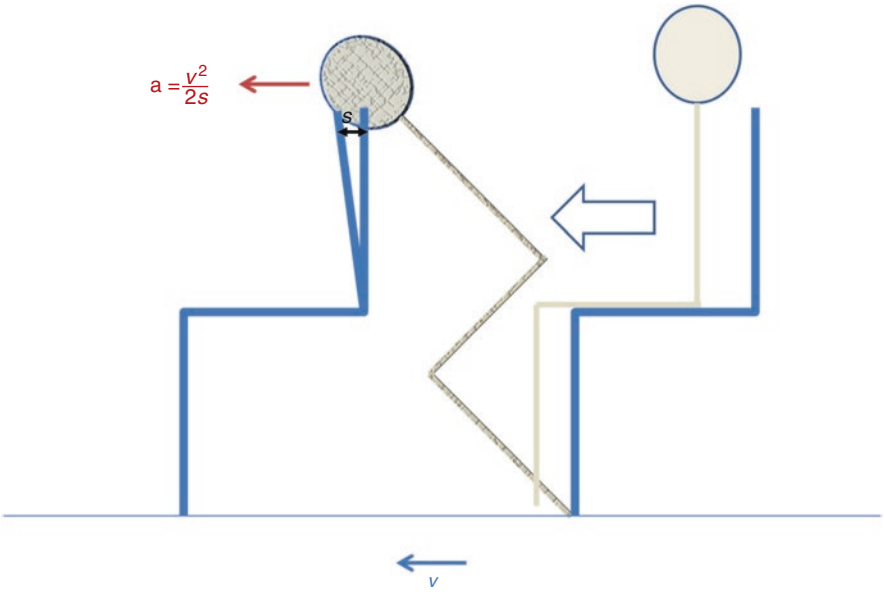

Fig. 1.4 Schematic of the accident reconstruction: Ravel was sitting without a seat belt, presumably on the back seat of the taxi. On impact, both the upper part of the body with the skull and the remaining part of the body (since he is not wearing a seat belt) move forward. In the process, Ravel hits the front seat back, which yields forward by the distance *s*; *v* velocity, *a* acceleration, see Sect. 1.4.1. A few of his teeth are knocked out. (Adapted from Otte (2021) with kind permission from Max Schmidt-Römhild Verlag, Lübeck)

1.4 Biomechanics

1.4.1 General Aspects

Already in the nineteenth century, at the very beginning of the development of automobiles, people—including physicians—were about to discuss the role and dangers of acceleration forces on drivers in automobiles. The first vehicle, from Carl Benz (1844–1929), the "Patent-Motorwagen Nummer 1" from 1886, achieved a maximum speed of 16 km/h. At that time, it was assumed that this "high" speed would cause serious medical problems due to the high speed itself (Elis 2010).

In a detailed review from Arthur Croft, in 1998, the biomechanics in low-speed rear impact collision is described. It has not lost actuality until today. Some of the following, therefore, is derived and summarized from Croft (1998).

Already in the 1950s, first crash tests were performed. Severy et al. (1955) studied anthropometric dummies and human volunteers. In this study, the speeds v of the car colliding with the rear end of the vehicle ahead were ranging from 7 to 20 mph (i.e., 11.3 to 32.2 km/h). Interestingly, the persons in the car were exposed to higher acceleration forces than the car itself: In rear-end car collisions with a Δv of 13.2 km/h, the heads of the test persons were exposed to accelerations of 5 g, whereas the car body itself had an acceleration of 2 g.

For the same Δv, the study by West et al. (1993) even measured acceleration forces of the head of human volunteers of about 15 g.

Over the years, more and more crash tests were performed, and many mathematical models were developed to calculate the acceleration forces on persons in cars who were exposed to different kinds of collision mechanisms.

The forces in whiplash injury—and the according literature on this—are relatively large. The literature is also heterogeneous: Some authors described crash tests with a certain speed, and some authors a crash with "acceleration" of a certain speed, which is not correct by definition, as acceleration describes a change of speed (Δv) per time.

Astronauts, e.g., are accelerated to speeds of about 30,000 km/h. This is, however, not harmful, since the change in speed (Δv) is performed over a larger time.

The acceleration a is described by the Eqs. (1.1) and (1.2a):

$$a = x \cdot g \tag{1.1}$$

and

$$a = \frac{\Delta v}{\Delta t} \tag{1.2a}$$

If a body moves out of rest constantly accelerated/decelerated, the following applies:

$$a = \frac{v}{t} \tag{1.2b}$$

and

$$s = \frac{1}{2} a t^2 \tag{1.3}$$

From Eqs. (1.2b) and (1.3) follows:

$$s = \frac{1}{2} a t^2 = \frac{1}{2} \frac{v}{t} t^2 = \frac{1}{2} v t \tag{1.4}$$

It follows:

$$t = \frac{2s}{v} \tag{1.5}$$

Substituting Eq. (1.5) into Eq. (1.2b), it follows:

$$a = \frac{v}{t} = \frac{v \cdot v}{2s} = \frac{v^2}{2s} \tag{1.6}$$

Substituting Eq. (1.6) into Eq. (1.1), it follows:

$$x = \frac{a}{g} = \frac{v^2}{2s \cdot g} \tag{1.7}$$

where

s: length of collision,
g: acceleration constant of the earth (9.80665 m/s^2), and,
x: (unit-less) multiplication factor ("the x-fold of g").

The following example may help to understand these equations in the car collision situation:

If we liked to determine the acceleration of the head, e.g., during a frontal collision at its contact with the windshield and we know that the windshield was moving 12.7 cm and the car moved with a speed of 40 km/h (=11.1 m/s) at collision, we can calculate x as follows (see Eq. (1.7)):

$$x = \frac{\left(11 \cdot 1 \ \frac{m}{s}\right)^2}{2 \cdot 0.127 \ m \cdot 9.80665 \ \frac{m}{s^2}} = 49.5$$

This means that the acceleration in this accident situation would achieve the 49.5-fold of the acceleration constant of the earth (g). By contrast, if the head hit the rigid metal frame of the window, which only moved, e.g., 1.27 cm, the acceleration of the head would be 10 times higher, i.e., 495 g. In this case, the injury would not be survived.

In Fig. 1.5 some scenarios for x, s and different v are shown. Table 1.2 gives general examples of accelerations in different situations.

The majority of rear-end car collisions are at speeds between 1 and 25 km/h, with rather minor damage on most cars. Olsson et al. (1990) showed that 18% of the investigated whiplash-injured patients were exposed to rear-end car collisions with speeds <10 km/h, 60% of the patients with speeds between 10 and 20 km/h, and 22% of the patients with speeds >20 km/h. These figures were approximately confirmed in an Australian study (Ryan et al. 1993). Interestingly, injuries due to rear-end car collisions occur more frequently with low speeds rather than with high speeds. This may be explained by the phenomenon that the collision with lower speeds is still relatively elastic, whereas the head constraints are not resistant during high Δv's. There is, however, no statistically significant correlation between the severeness of the accident and the clinical outcome.

The awareness of a collision in most cases reduces the injury grade markedly. According to Severy et al. (1955), this is caused by highly reduced forces on the

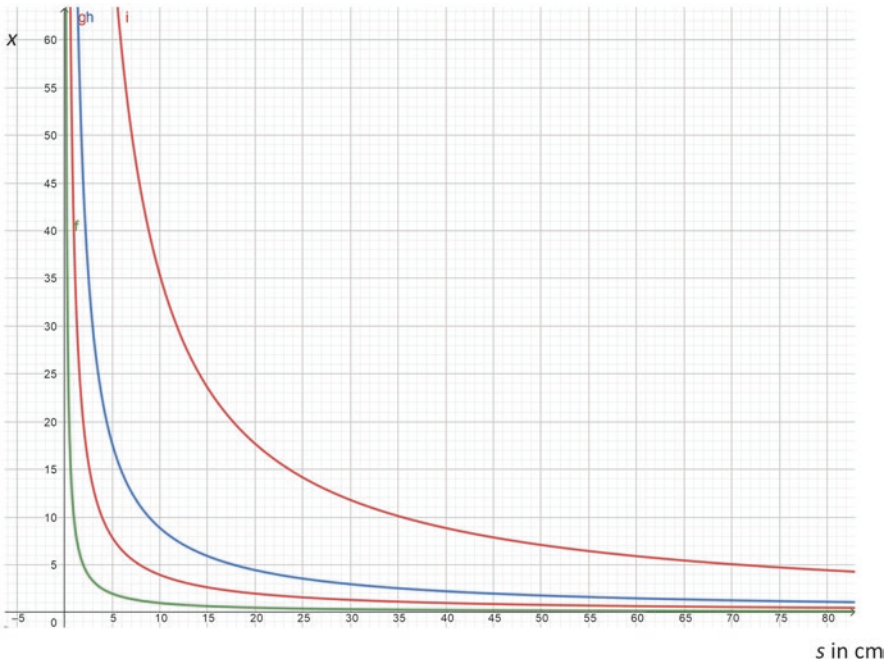

Fig. 1.5 Some scenarios for x, s and different v are shown for the function $x(s) = \frac{v^2}{2s \cdot g}$. s is plotted in cm on the x-axis; x is plotted on the y-axis. From left to right, the curves are drawn for different speeds v: 5 km/h (green, far left), 10 km/h (orange), 15 km/h (blue), and 30 km/h (red, far right). Already with 30 km/h and s = 10 cm, x would be 35.4. This is already a very high acceleration, which would almost certainly have ended fatally. Created with *GeoGebra*, version 6.0.634.0-wgraphing

Table 1.2 General examples of accelerations in different situations

Situation	Acceleration
Normal ride in car	0.3 *g*
Pilot of a formula 1 Race car	1–1.5 *g* at the start; Up to 5 *g* in curves
Flight in passenger aircraft	Up to 1.5 *g*
Astronauts	3–4 *g* at the start; 0 g (gravityless) on their orbit around the earth[a]
Roller coaster ride	Short-term up to 6 *g*

Figures from Hannemann, 2009

[a]If a rocket takes off from the earth's surface, it must travel at a speed of at least 7.9 km per second in order to enter the earth's orbit, that is 28,440 km/h

head. These forces were, e.g., reduced by the car drivers by actively pushing themselves back to the seat and by activating their muscles.

In the year 1969—the year of the landing on the moon—head restraints became mandatory for all automobiles in the USA and a few years later, in 1974, also in Germany. Head restraints help to avoid cervical injuries. Nevertheless, this protection is greatly diminished if the distance of the head from the head restraint is more than 5 cm at the beginning of the injury, as Mertz and Patrick could show already in 1967. In a study from Olsson et al. (1990) symptoms in the neck and cervical region markedly increased if the head distance from the head restraint was more than 10 cm. The majority of head restraints are, however, incorrectly positioned. In addition, there is the problem of ramping, i.e., the upward movement of the body in the seat during a collision. Therefore, any mathematical calculations of collision sequelae are only idealized models. Reality may show much larger injury of head and neck than previously calculated.

Following the simple rules of physics, the injury grade in a rear-end car collision tends to be proportional to the size of the car hitting the front car and to negatively correlate with the size of the front car which is hit at its rear end.

1.4.2 Protection Systems to Avoid Whiplash Injury

Over the past years, various automobile industries have developed protection systems against whiplash injury, which diminish the acceleration forces on the neck and the spine occurring already in rear-end car collisions with relatively low speeds. These systems are, e.g., "WHIPS," the "active head restraint," shock-resistant bumper systems, or the rear-end car collision assistance systems with radar sensors, which activate seat belts and position the head restraints correctly.

Although air bags (in the steering wheel) are not activated during pure rear-end car collisions, many of the patients with cervical spine injury have been involved in accidents with activation of the air bag. The air bag can have positive and negative implications on whiplash injury; its usefulness in terms of the whiplash syndrome is, however, controversially discussed. There are also commercially available head restraints with self-inflating air bag systems.

The impact of all of these new protection systems on the severity of the accident cases needs further investigation.

1.4.3 Sequence of Phases During a Typical Whiplash Injury

After this general introduction in biomechanical processes in rear-end car collisions, we would now like to discuss the sequence of phases during a typical whiplash injury.

Two of the important early contributions to understanding this sequence of phases during whiplash injury, which is caused by low speeds, are from McConnell et al. (1993, 1995). The group investigated healthy adult men in unbraked crash tests with Δv's of <3.2 km/h till 10.9 km/h. Cars with different weight were used, and the healthy volunteers undertook different tests during several days. Some of the volunteers complained about intermittent neck pain or other symptoms due to the tests, whereas none developed long-term complaints. The collision tests and the complex acceleration and deceleration processes during the collisions were recorded on high-speed films. In the first study from 1993, an exemplary test at 7.8 km/h speed recorded the following sequence of whiplash phases (Fig. 1.6):

1. *Initial phase* (0–100 ms): The crashed car moved beneath the test person compressing the seat back cushion. At first, this caused a movement of the hips and the low back to the front, whereas at the same time, the upper part of the seat back cushion began a flexion to the rear end due to the weight of the torso.
2. *Principal forward acceleration* (100–200 ms): In this phase, the seat back cushion achieved its maximum flexion to the rear end of approximately 10°, as compared to the initial position. The volunteer moved to the upper front, and the cervical region was extended axially to the upper rear end. At the same time, the head rotated to the rear end. At 160 ms, the vertical movement of the torso started to pull the neck to the front, while the head continued to move into extension position.
3. *Torso recovery/head overspeed* (relatively higher speed of the head compared to the torso; 200–300 ms): At 200 ms, the maximum extension of head and neck and the maximum vertical movement were achieved. At 250 ms, the head began its forward movement and the torso moved downwards along the seat back cushion, while the seat back cushion had moved back to its initial position.
4. *Head deceleration/torso rest* (300–400 ms): In this phase, the declination of the head was complete and the torso was moving with the car speed. At the end of this phase, the active deceleration by intended intervention of the volunteer was achieved. The head of the volunteer gradually moved back to its initial position.
5. *Restitution phase* (400–600 ms): At 450 ms, all body parts were moving with the car speed. Movements from the collision were nearly finished.

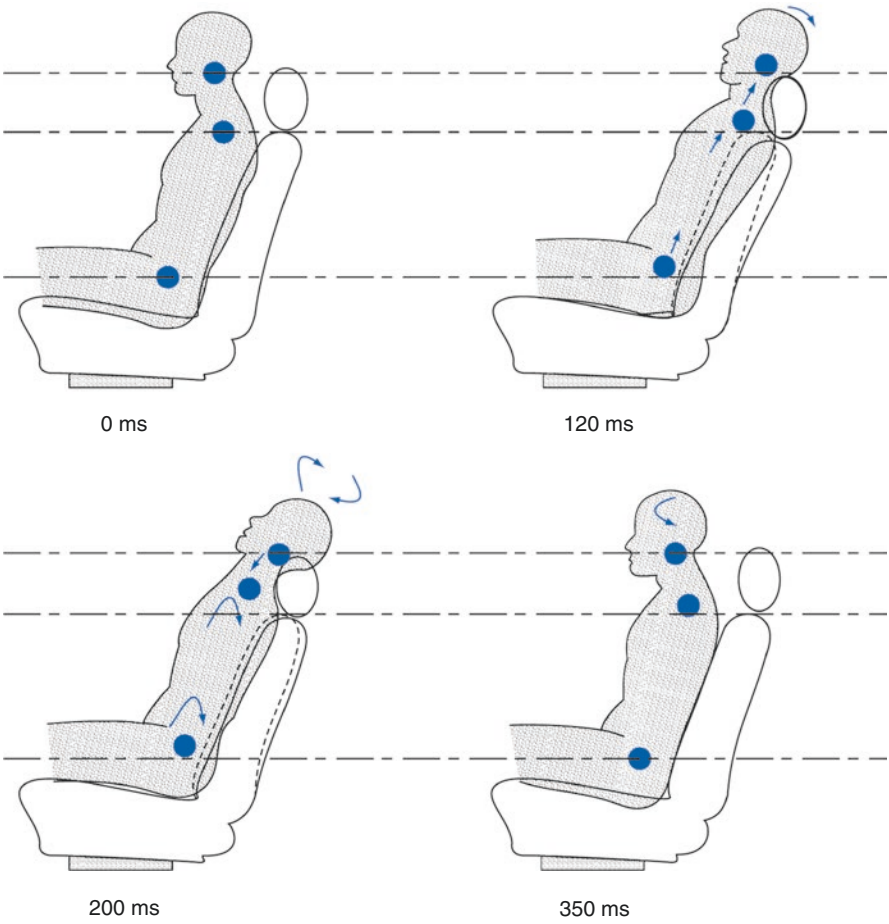

Fig. 1.6 Sequence of phases in whiplash injury modified from McConnell et al. (1993). For details, see text. (Adapted from Otte (2001d) Das Halswirbelsäulen-Schleudertrauma: Neue Wege der funktionellen Bildgebung des Gehirns—Ein Ratgeber für Ärzte und Betroffene, Springer, Heidelberg)

Although this fascinating study for the first time revealed the dynamics of whiplash injury relatively precisely, the following potential pitfalls must certainly be realized:

- Brakes were not used.
- Volunteers tried to be correctly in position.
- Volunteers were aware of the collision.
- Only healthy men, no females or children, were included.

Many other studies followed to understand the kinematics of neck structures during a whiplash trauma, including various methods (mathematical models, anthropometric dummies, animals, cadavers, and human healthy volunteers). The studies are all fairly consistent. Svensson et al. (1993) and Grauer et al. (1997), however, replaced the former hypothesis of cervical hyperextension as the mechanism of whiplash injury (Macnab 1964) by the "S-shape" concept, in which the movement of the head and neck remains within physiological range, but the initial cervical retraction produces a non-physiological curvature, an S-shape. This is the moment when the injury takes place.

The current opinion on the sequence of phases in whiplash injury is summarized in Fig. 1.7 (from Vállez García et al. 2014).

Interestingly, already in the work from Severy and colleagues (Severy et al. 1955), the whiplash sequence for one cycle was measured by electric accelerometers (Statham Model 120). In one of the 5 runs, the rear car that was driven by a human volunteer crashed with a pre-impact velocity of 19.8 mph (i.e., 31.9 km/h) into the front car equipped with a dummy. The acceleration on the rear cars driver head was 8.0 *g*, the acceleration on the front cars dummy head was 11.4 *g* (whereas the car itself only had 6.3 *g*). The time was measured from zero time, the instant the cars made contact. For this case, the following head accelerations and subject responses were reported—note that in this study the cars did not have head restraints, therefore the intervals are different as in the scenarios shown in Figs. 1.6 and 1.7 (Severy et al. 1955):

- At 20 ms: 0 *g*, "Head erect";
- At 100 ms, −1.0 *g*, "Head reaction due to force application below body center of percussion of the subject for seated position";
- At 235 ms, +8.3 *g*, "Extreme dorsi-flexion of head";
- At 287 ms, 0 *g*, "Head has accelerated to car velocity so head velocity becomes constant with head flexed 86° rearward on its way forward";
- At 370 ms, −4.0 *g*, "Head 11° aft of erect, swinging forward with increasing acceleration due to restitutional forces of seat back and neck";
- At 580 ms, −3.0 *g*, "Head strikes visor above windshield";
- At 960 ms, 0 *g*, "Body is thrown back against seat";
- At 1030 ms, 4.5 *g*, "Seat back re-accelerates body to cause a second but less severe head-snap".

Severy et al.—although already in 1955 but still highly up-to-date—point out that the whiplash injury pattern can be "significantly influenced by any or all of the following factors: (a) Speed of contact of the two vehicles. (b) Type of cars: mass and collapse characteristics of contacting sections. (c) Height and strength of seat back. (d) Human body variations including height, weight and age as well as the posture of the individual. (e) Defensive action, if any, taken by motorist when forewarned of imminent collision."

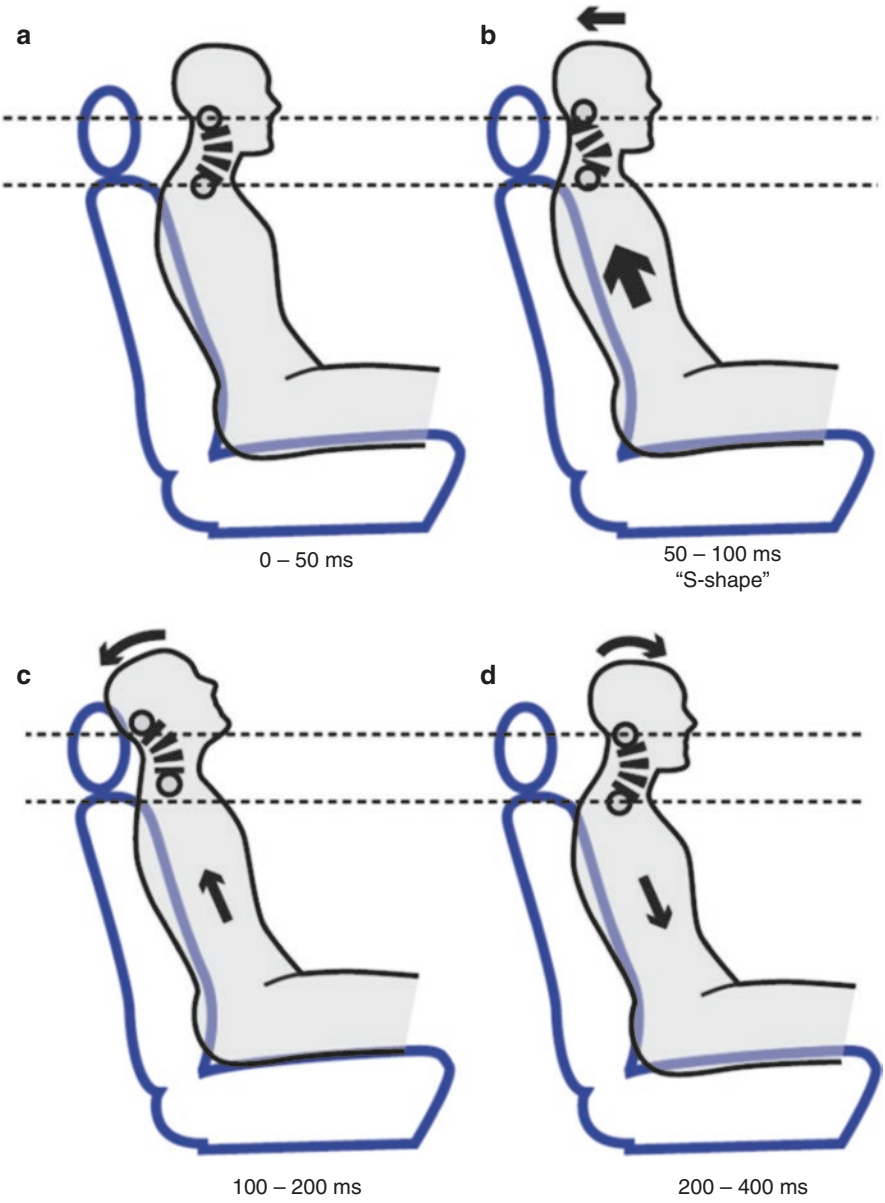

Fig. 1.7 Sequence of phases in whiplash injury as summarized by Vállez García et al. (2014). (**a**) 0–50 ms: After the impact there is no motion or body response. (**b**) 50–100 ms: The torso, pushed by the seat, is pushed forward and upward; meanwhile, the head remains stationary due to the inertial force. The ascending movement of the trunk compresses the cervical spine, which, around 60 ms after the impact, undergoes an "S-shape" deformation, with the lower cervical segments exceeding physiological extension and the upper cervical segments flexion. (**c**) 100–200 ms: The head reaches a peak movement in extension of 45°. (**d**) 200–400 ms: Head, neck, and trunk start to descend, and approximately 400 ms after the initial impact, the head achieves its maximum forward displacement. (Adapted from Vállez García et al. 2014)

1.4.4 Timing of Neck Muscle Contraction

As mentioned above, it is crucial whether the driver in the rear-end crashed car is aware or unaware of the impeding collision. According to Mertz and Patrick (1967) and Stemper et al. (2005, 2006), aware occupants obtain maximum neck muscle contraction before the impact leading to elimination of the S-shape curvature and decrease in the extension magnitude and soft tissue distortion. In the situation with unaware occupants, the muscular reflex contraction has minimal effect, since the maximum contraction levels are achieved after injury time (S-shape) (Kumar et al. 2005). The awareness or expectancy of the incoming collision is essential in the whiplash process; despite this fact, it was rejected as predictive factor (Walton et al. 2009). It is known that 70–80% of the patients suffering from whiplash injury were unaware of the incoming collision (Hartling et al. 2002; Hendriks et al. 2005; Atherton et al. 2006). Furthermore, when pain was not the only outcome, a correlation was noted between being unaware of the incoming collision and a poor recovery 12 weeks after injury (Hendriks et al. 2005).

1.4.5 Finite Element Method

The finite element method (FEM) is a complex numerical mathematical procedure used in many different areas of engineering, e.g., fluid mechanics, acoustics, statics, dynamics or deformation and acceleration physics (Brand 2016). Of particular interest to our problem is the area of statics, which deals with tensile stresses, strains, and deformations, among other things. Here, an object is first decomposed into a finite number of small and simple elements and thereby transformed into a mesh (with nodes). Force, translation vectors and global stiffness matrix are calculated via a linear or non-linear system of differential equations using FEM software.

The Austrian-US American mathematician Richard Edler von Mises (1883–1953) contributed with his so-called strain energy hypothesis to the fact that one can calculate the von Mises equivalent stress for a 3D stress state, which can be used to determine the load limit of a material for combined loads.

Already in 2005, Teo et al. developed a 3D head-neck FEM model to analyze the head-neck responses during whiplash. They could show that the lower cervical vertebrae (especially C6-C7) were particularly affected by the whiplash injury. We could easily reproduce the input acceleration over time curve and the predicted maximum von Mises stress history of C6-C7 of this study (Fig. 1.8a) using the C6-C7 measurement point (Fig. 1.8b).

By purely using FEM, we could also simulate the input acceleration over time curve from the aforementioned, very elaborate early study by Severy et al. (1955), who utilized human volunteers and anthropometric dummy subjects instrumented by mechanical and electrical accelerometers undergoing rear-end collisions with a 1941 Plymouth to strike the rear of a 1947 Plymouth at speeds from 7 to 20 mph without headrests. Remarkably, the theoretical FEM calculations showed nearly exactly the curve in the real life situation of 1955 (Otte et al., unpublished data).

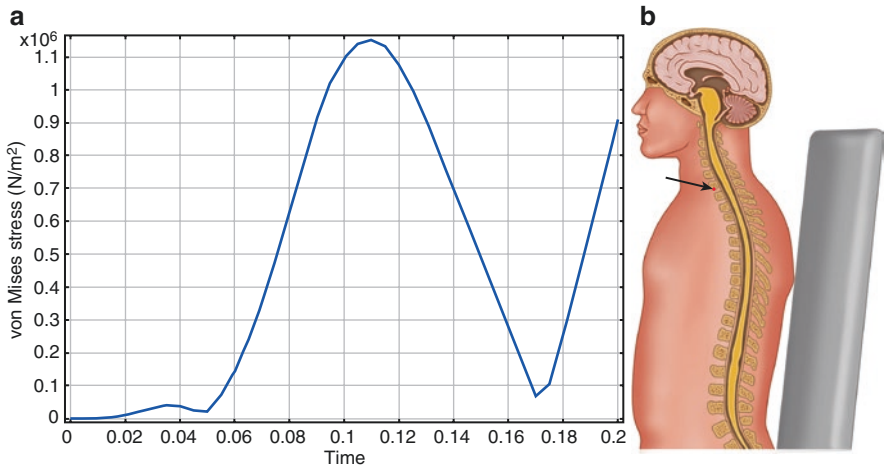

Fig. 1.8 (**a**) FEM simulation of the predicted maximum von Mises stress in the C6-C7 disc during whiplash with 200 ms acceleration/deceleration duration (without headrests) according to the study setting of Teo et al. (2005), von Mises stress in $N/m^2 \cdot 10^6$, time in s; (**b**) The measurement point in our FEM simulation model, see the red point indicated by the arrow

This indicates to us that the FEM analysis could be the right way for calculations on any future whiplash model.

1.4.6 Woodpecker's Brain Trauma Protection System

Recent research has focused on the biomechanics of the woodpecker. In this context, FEM analysis and Material Point Method were used to investigate the forces on the skull and the shear forces on the brainstem (Wang et al. 2011; Liu et al. 2015). Indeed, in woodpeckers, more than 1000 *g* act at a speed of about 6 to 7 m/s during the pecking process, depending on the bird species. If the woodpecker were to get a headache from this activity, which it performs about 12,000 times a day and serves to acquire its food, it would stop immediately. But since this is not the case, there must be a mechanism that protects the brain from traumatic brain injury. Already for mild traumatic brain injury, the study of shear stress in the brainstem has proven to be the best indicator of brain injury (Zhang et al. 2004). Therefore, this approach was also used by Liu et al. 2015.

It has been found that in the woodpecker various endoskeletal factors distribute the forces on the skull in such a way that the cervical spine as well as the brainstem and the rest of the brain remain protected (Fig. 1.9). On the one hand, protection is provided by a narrow subdural space, a smooth skull and a straight pointed beak with elongated keratin scales, which reduce the impact energy by shearing and which are unequal in length between the top and bottom beaks (Fig. 1.10). On the

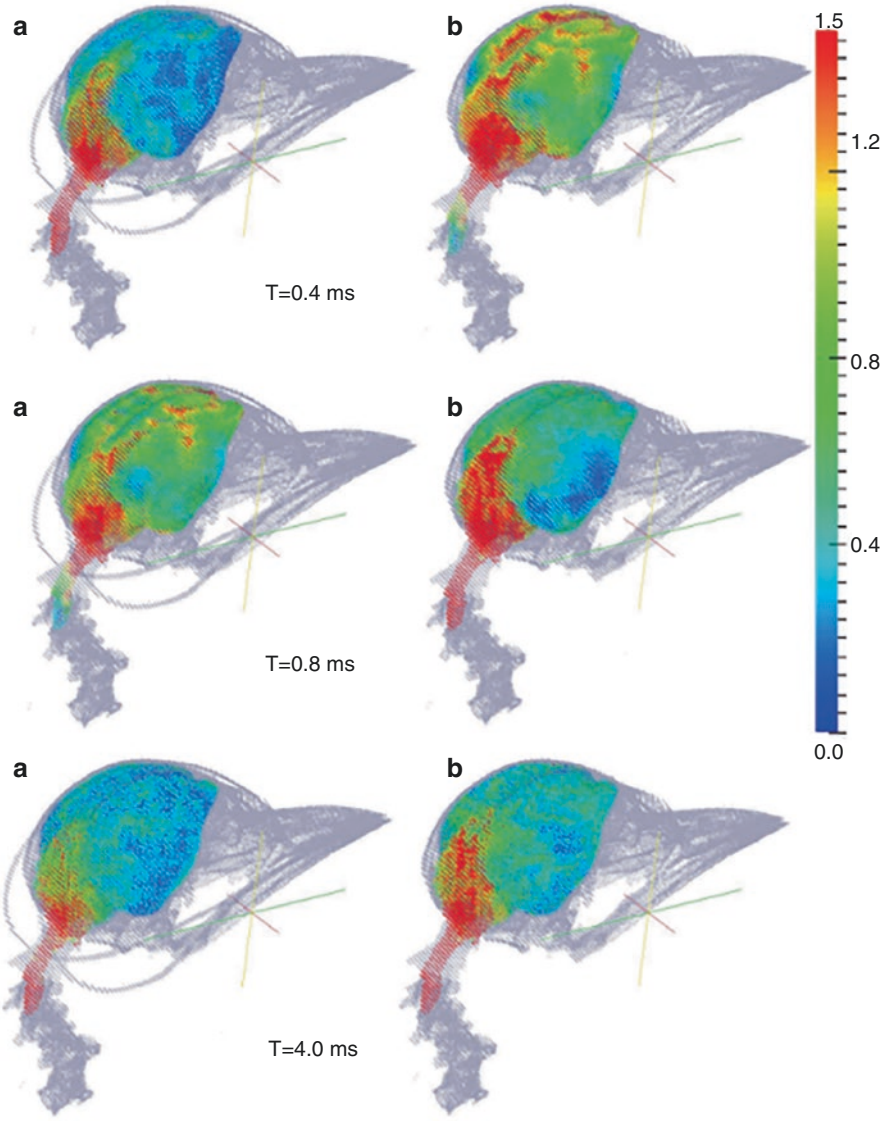

Fig. 1.9 Shear stress contours of the woodpeckers brain at different time points under 1 m/s impact velocity, color bar in kPa; (**a**) model with the help of the hyoid bone, (**b**) model without the help of the hyoid bone. (Copyright 2015 by Liu et al., doi:https://doi.org/10.1371/journal.pone.0122677. Published by PLos One under the terms of the Creative Commons Attribution License CC BY 4.0, which permits unrestricted use, distribution, and reproduction in any medium)

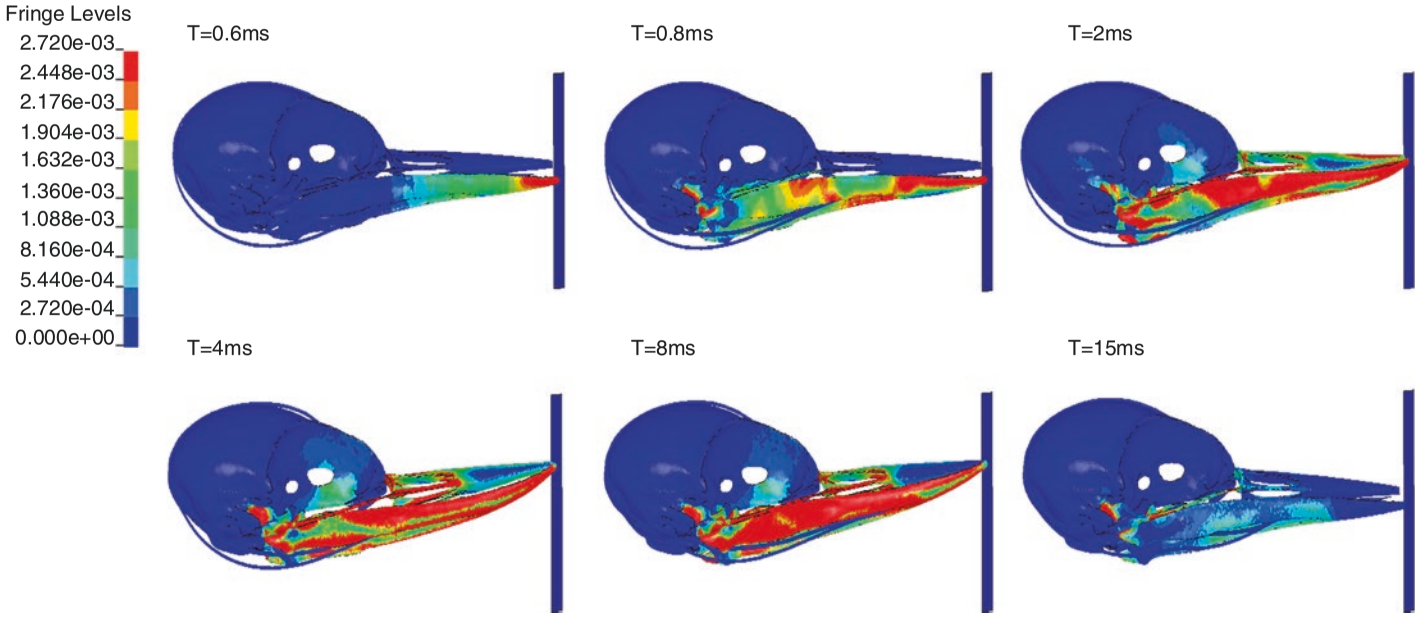

Fig. 1.10 Stress distribution of the woodpecker's head during pecking showing the difference between upper and lower beak. (Copyright 2011 by Wang et al., doi:https://doi.org/10.1371/journal.pone.0026490. Published by PLos One under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium)

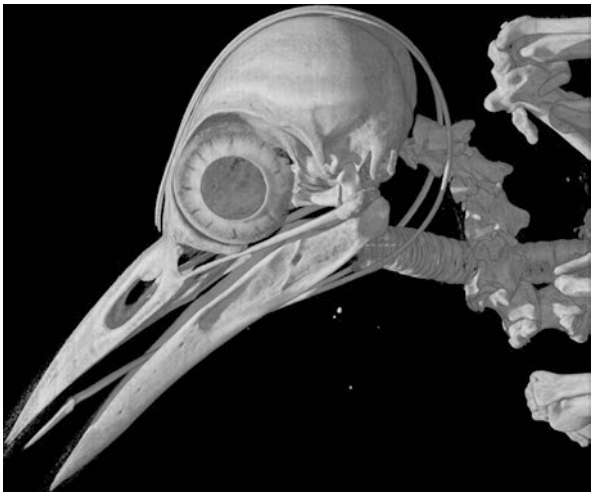

Fig. 1.11 High-resolution X-ray computed tomography scan of the head and neck region of the golden-fronted woodpecker (*Melanerpes aurifrons*). (Source: DigiMorph Staff, 2004, "Melanerpes aurifrons" (On-line), Digital Morphology. Accessed July 11, 2021 at http://digimorph.org/specimens/Melanerpes_aurifrons/ with kind permission by the copyright holder, Dr. Timothy Rowe from the Digital Morphology Group, in conjunction with The University of Texas High-Resolution X-ray Computed Tomography Facility)

other hand, the protection is supported in particular by a long hyoid bone, which in woodpeckers—unlike in humans—anatomically starts in a remarkable way at the end of the tongue, passes through the mandible, where it divides into two parts, thus encircles the skull, units into one, and finally ends at the right nostril (Fig. 1.11). This absorbs or cushions the forces acting through the beak (Fig. 1.12).

The considerations on the biomechanics of the woodpecker are certainly of great interest for the development of protective systems to reduce the consequences of brain trauma and are therefore worth mentioning.

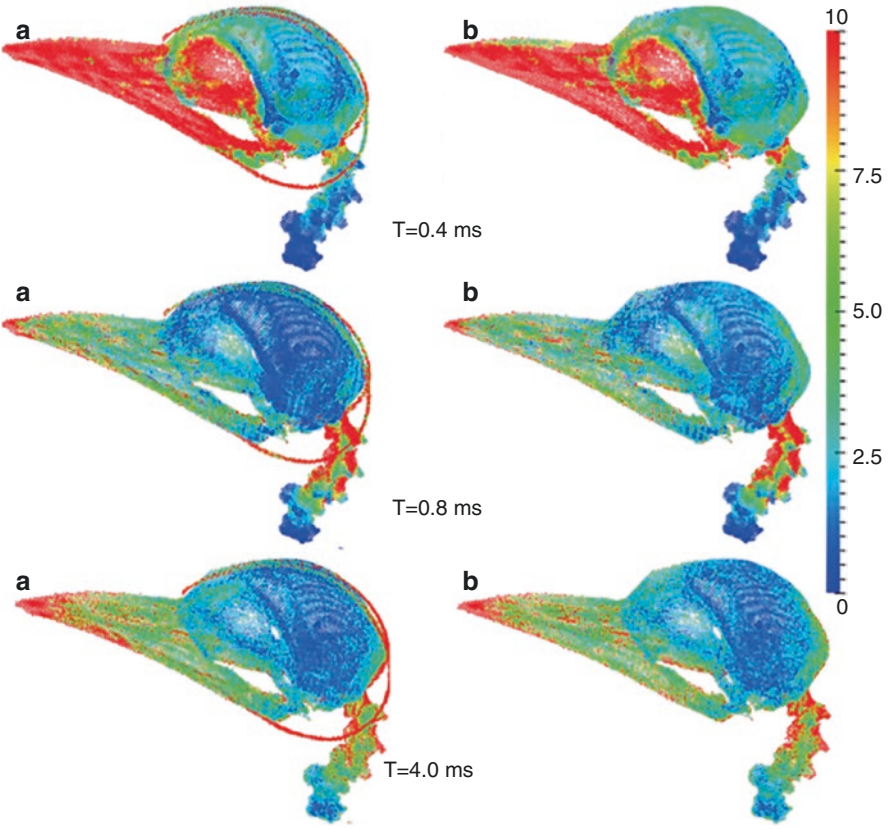

Fig. 1.12 von Mises stress contours of the woodpeckers endoskeleton at different time points under 1 m/s impact velocity, color bar in 10^5 Pa; (**a**) model with the help of the hyoid bone, (**b**) model without the help of the hyoid bone. (Copyright 2015 by Liu et al., doi:https://doi.org/10.1371/journal.pone.0122677. Published by PLos One under the terms of the Creative Commons Attribution License CC BY 4.0, which permits unrestricted use, distribution, and reproduction in any medium)

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Diagnostics

2

2.1 Diagnostic Procedure After Whiplash Injury

The usual diagnostic procedure in whiplash injury is illustrated in Fig. 2.1.

Unfortunately, methods assessing the condition of the *brain* are frequently not utilized and also still not intended in the emergency supply of cervical spine injuries (e.g., Leidel 2018). These methods are:

1. Computerized tomography (CT) and magnetic resonance imaging (MRI) of the brain: With these methods usually no pathological cerebral findings are found in whiplash injury.
2. Neuropsychological tests: The role of neuropsychological tests for this indication is at present still being discussed.
3. Functional neuroimaging: Functional neuroimaging devices are quite sensitive measuring instruments, which are of help in the puzzling diagnosis of the late whiplash syndrome subsequent to a whiplash injury. Especially functional neuroimaging using the nuclear medicine devices single-photon emission tomography (SPET) or positron emission tomography (PET) in combination with stereotaxic brain slice delineation (e.g., Talairach and Tournoux 1988, 1993) and statistical parametric and nonparametric mapping (SPM) software developed by Friston et al. (1991, 1995) is currently of essential value. In addition, functional MRI, magnetic resonance spectroscopy, superconducting quantum interference device (SQUID) magnetoencephalography (MEG), and the newer hybrid imaging technologies—such as PET/CT, SPET/CT, or MR/PET—may be future methods of functional neuroimaging interest in this indication. We have excluded a detailed description of functional neuroimaging devices from this book. A detailed and state-of-the-art review on the basics of these—including image analysis tools—can, e.g., be found in Otte (2001b), Otte and Halsband (2006), and Dierckx et al. 2014, 2021a, b, c. Briefly, however, the following should be said here about SPET and PET, the two routine instruments in nuclear medicine:

A. Otte, *Functional Neuroimaging in Whiplash Injury*,
https://doi.org/10.1007/978-3-030-91255-0_2

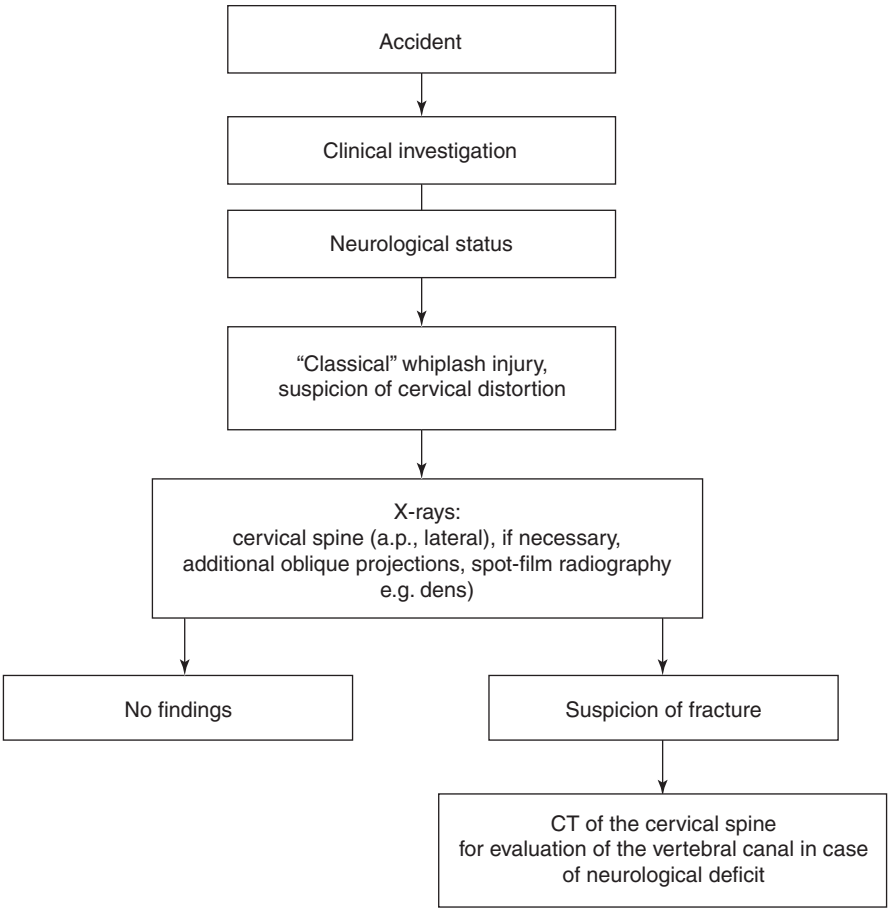

Fig. 2.1 Usual diagnostic procedure in whiplash injury. Imaging of the brain is routinely not performed. (Strongly modified from Jörg and Menger (1998), Schmid (1999), adapted from Otte et al. (eds) (2004) Nuclear Medicine in Psychiatry, Springer, Heidelberg)

In SPET, a rotating gamma camera moves at least 180 degrees around the longitudinal axis of the patient in defined angular positions (Fig. 2.2). SPET cameras are equipped with one, two, or more heads. A three-headed camera has shorter acquisition times (approximately 20 min for a brain examination) and significantly higher resolution than a single-headed camera. An image is taken at each angle and digitally processed. Various filter systems—such as Metz, Ramp, Wiener, or Butterworth filters—help to filter out the "background noise." Incorrect filtering can lead to a deterioration in image quality. PET is based on the effect of the so-called annihilation radiation of positrons, which emits two gamma quants at an angle of 180 degrees, each with an energy of 511 keV. An image signal is generated only when two opposite detectors simultaneously (coincidentally) detect scintillation. Therefore, the PET scanner generally con-

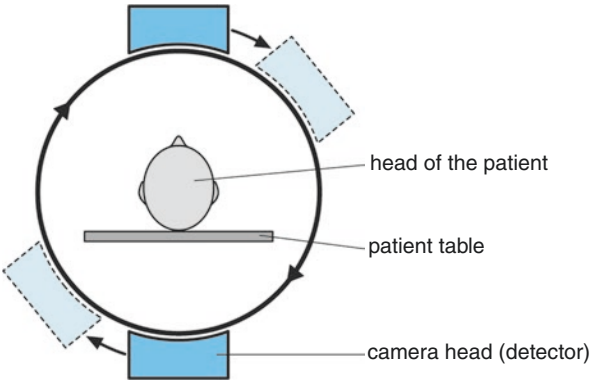

Fig. 2.2 Principle of a SPET camera: In the double-headed SPET camera outlined here, two opposing camera heads rotate around the patient emitting gamma rays. An image is taken in each angular position. (Adapted from Otte (2001b))

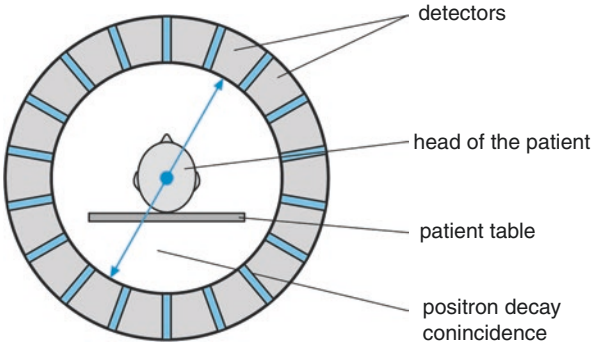

Fig. 2.3 Principle of PET: In PET, simultaneous events, so-called coincidences, are measured. This enables the exact spatial assignment of a signal. (Adapted from Otte (2001b))

sists of a solid ring containing many small detectors capable of measuring these coincidences (Fig. 2.3). Recently, less expensive rotating partial ring scanners have also become available. Unlike SPET, PET detectors do not contain collimators that would focus the gamma rays in one direction. The coincidence circuit enables a three-dimensional and temporal assignment of the measured signal. It is noteworthy that the history of SPET and PET, which is closely linked to the history of nuclear physics, especially in its early years, is young: In 1947, Kallman discovers the ability of crystals to absorb gamma rays and emit flashes of light (scintillation; lat. Scintilla: the flash of light); he builds the first crystal detector. In 1951, Benedict Cassen succeeds in imaging the activity distribution using a rectilinear scanner. Hal O. Anger builds the first scintillation camera (gamma camera) in 1958, incorporating a collimator and photomultiplier; this development is the basis for both, SPET and PET. In 1962, Harper and Lathrop introduce technetium (^{99m}Tc) into diagnostics, which is used to refine imaging on the Anger camera. In the same year, Rankowitz and Robertson give the first description of the PET technique using a detector ring. This is followed in 1963 by Kuhl and Edwards' first description of the SPET technique. Although SPET and PET were invented in the early 1960s, it was to be several years before these techniques found their way into routine clinical use. The main problem was that

computer technology was still in its infancy. This explains why Ommaya's early experiments in rhesus monkeys (Ommaya et al. 1968), as described in Sect. 1.1.1, could be performed not only without the possibility of CT, but also without a possibility for functional neuroimaging by SPET or PET. Now, however, rapid advances in electrical engineering, medical engineering and computer science over the last half century have given us a much better framework from which to study functional alterations of the brain.

4. Other imaging devices, such as electroencephalography (EEG) or functional near-infrared spectroscopy (fNIRS), are important diagnostic procedures in neurosciences and could be helpful in the diagnosis of whiplash patients in future, given the improving developments of medical technology on the spatial resolution of these devices. Functional NIRS can measure oxygenized, deoxygenized, and total hemoglobin changes in real time (Chance 1991; Chance et al. 1993) and may be combined with cognitive tasks (psychological stress tests) and electromyography (EMG)-controlled upper neck muscle endurance tests (Otte et al. 2013), an approach in which it is hypothesized that patients with chronic pain, caused by either non-traumatic or traumatic mechanisms, have an increased muscle fatigue as compared to healthy subjects, see Sect. 4.2.

Recently, a mismatch between aberrant information from the neck muscles (ascending afferents from the upper cervical segments C1–C3) and the vestibular and visual systems, integrated in the mesencephalic periaqueductal gray and adjoining regions, has been discussed (Vállez García et al. 2014; discussed in Otte et al. 2014) (Fig. 2.4). Therefore, functional imaging studies of the brain and of the cervical soft tissue may indirectly show this presumed injury-induced mismatch.

2.2 New Iteration Algorithms

Over the last 10 years, software technologies have helped to create iteration algorithms for SPET, which convincingly improve the signal-to-noise ratio of reconstructed images. These new iteration algorithms, such as ordered subset expectation maximization (OSEM) or depth response ordered subsets expectation maximization (DROSEM), have meanwhile replaced the conventional filtered back projection. Perfusion studies with ^{99m}Tc-labeled ethylene biyldicysteinate dimer, Neurolite™ (ECD), or hexamethyl propylene amine oxime, Ceretec™ (HMPAO SPET) (Fig. 2.5) have become attractive and cheap in the clinical routine. For the diagnostics of potential functional alterations in whiplash injury, they are as recommendable as glucose utilization studies by fluorodeoxy-D-glucose (Fig. 2.5), glucose analogon; labeled with the positron emitter fluorine-18, it is used in PET as glucose metabolism marker (^{18}F-FDG PET).

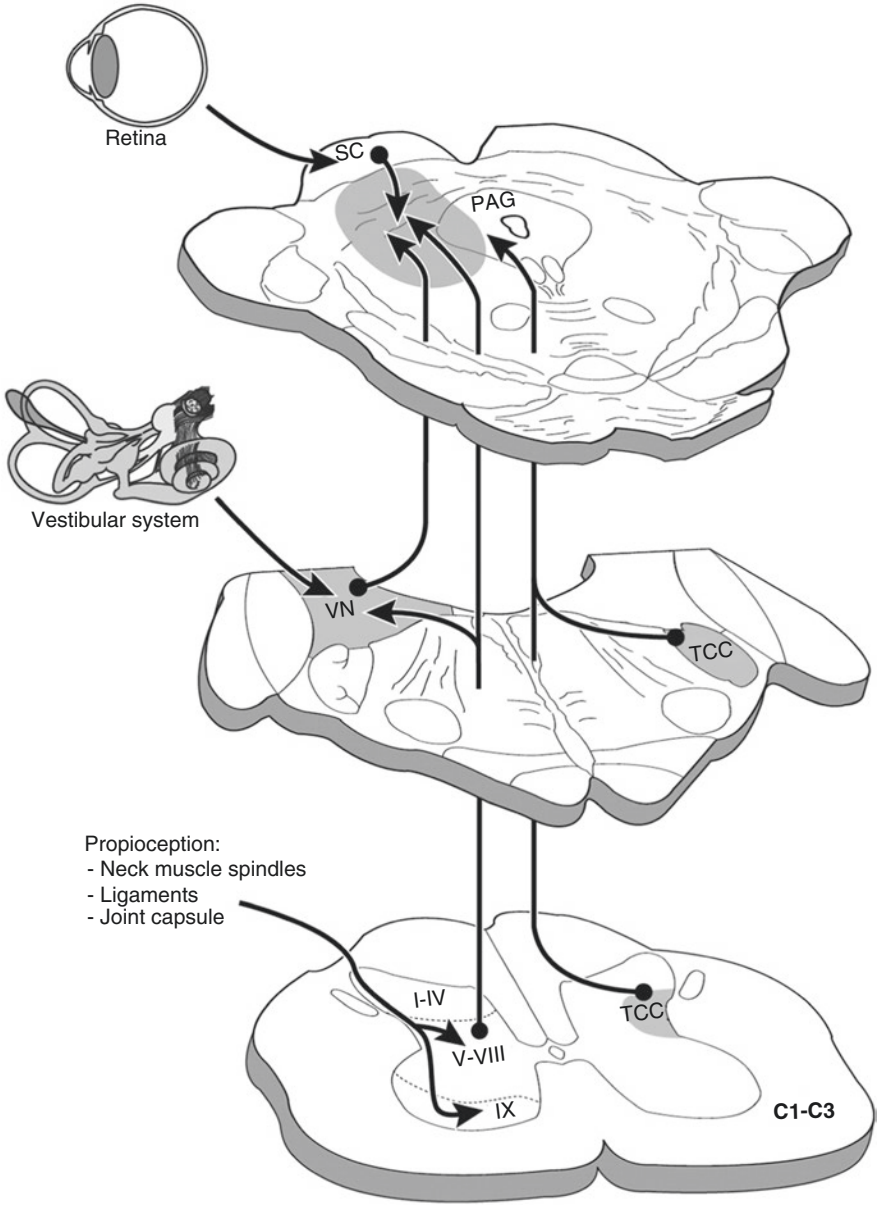

Fig. 2.4 Ascending afferents from the upper cervical segments (C1–C3) to the peraqueductal gray (*PAG*) and its adjacent regions. *TCC* trigeminocervical complex, *VN* vestibular nuclei, *SC* superior colliculus. (Adapted from Vállez García et al. 2014)

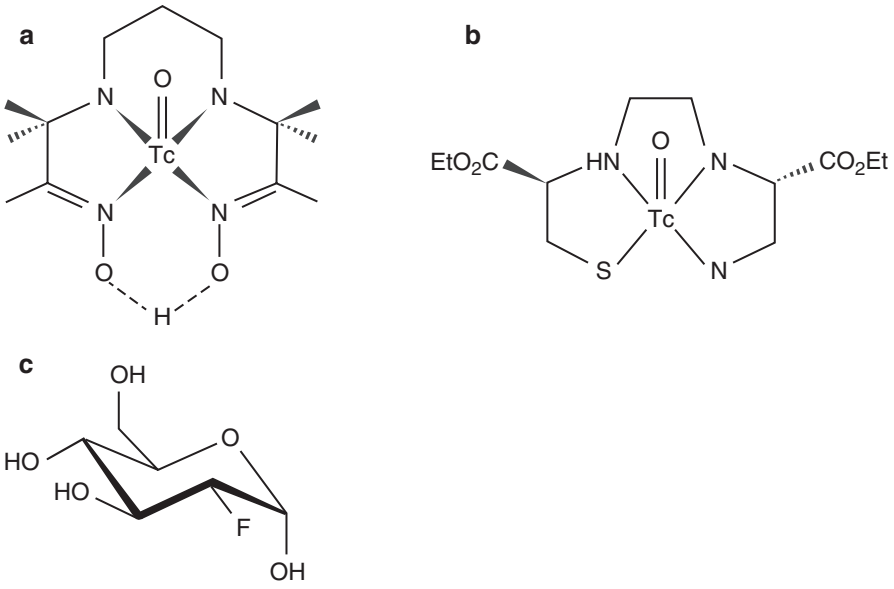

Fig. 2.5 Structural formula of HMPAO (**a**), ECD (**b**), and FDG (**c**)

2.3 Stereotaxic Atlas of Talairach and Tournoux

The initial basis for SPM analysis of brain alterations is the coordinate system according to Talairach and Tournoux. As this coordinate system has been used for SPM over many years, we would, therefore, like to describe this atlas and the idea behind it in more detail.

Talairach and coworkers had already finished an atlas for the basal ganglia of the human brain in 1958. The first edition of the whole brain was published in 1967 entitled *Atlas d'Anatomie Stéréotaxique du Télencéphale*.

In this atlas, a new idea was proposed: a proportional stereotaxic grid showing the anatomy of the brain in a standardized coordinate system. For this atlas, Talairach studied in total 20 full brains and 100 hemispheres, which he compared with 400 neuroradiological assessments. For the anatomical sections, the AC-PC line (line between anterior and posterior commissure) determined by the neuroradiological image data was taken as the reference line and anatomical slices were cut in parallel to this line. From this, a 3D grid was created, which is defined by three main lines and six reference voxels (Fig. 2.6).

According to this coordinate system, the Talairach reference brain was defined.

The Talairach atlas shows all brain slices of the three dimensions of the Talairach coordinate system. In its version from 1988, it has become a European standard. In the first edition (1967), the atlas was produced from six brains of different sizes in order to demonstrate the validity of the stereotaxic coordinate system. This atlas comprised 32 sagittal slices from the hemispheres of two brains, 22 and 24 coronal

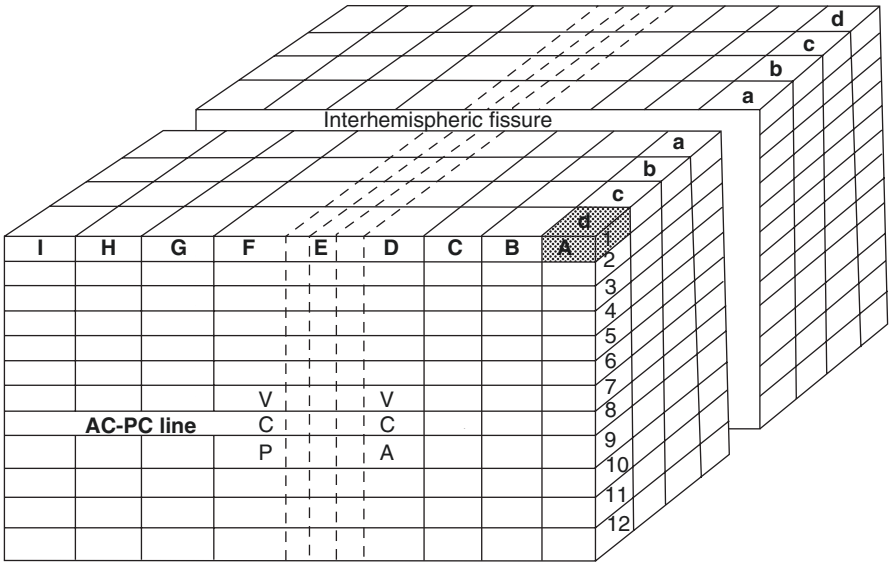

Fig. 2.6 Talairach and Tournoux atlas 3D grid for the brain from 1988. AC-PC line: line between anterior and posterior commissure of the brain. The brain is "pressed" into this volume box, accurately enabling to define the coordinates of each voxel on a standardized basis. (Adapted from Otte (2001b))

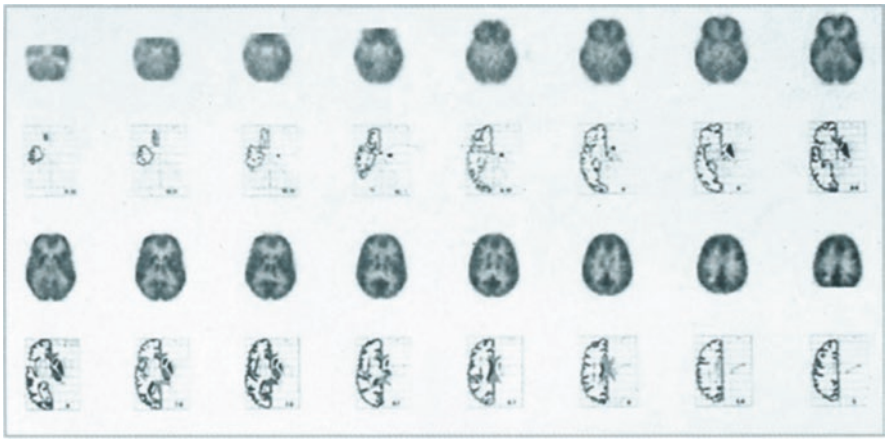

Fig. 2.7 Example from the *Talairach and Tournoux* atlas. Transversal slices from the digitized atlas are exhibited with the corresponding PET slices, which are normalized according to the *Talairach* atlas. (Modified from Otte (2001b))

slices from two further brains, and each 18 transversal slices from a third pair of brains. By contrast, in the 1988 version of the Talairach atlas, only one brain of a mid-European woman is taken as the anatomical reference. In Fig. 2.7, an example from the Talairach atlas is shown along with the corresponding PET slices in transversal projection.

2.4 Other Stereotaxic Atlas Systems

2.4.1 Computerized Brain Atlas

The Computerized Brain Atlas (CBA) by Greitz et al. (1991) is also based on the Talairach coordinate system. The CBA software was redesigned to a user-friendly new version by Thurfjell in 1994, although compared to SPM it is, as we think, relatively complicated to use.

2.4.2 Montreal Atlas

Many current studies normalize to the Montreal Neurological Institute's stereotactic template, the so-called MNI Average Brain (305 MRI) Stereotaxic Registration Model: In contrast to using a single subject brain as a template as in the 1988 Talairach atlas, Evans and coworkers introduced the concept of a statistical MRI atlas for brain mapping based on an average of 305 T1-weighted MRI scans, linearly transformed to the Talairach space (Evans et al. 1992a, b, 1993).

To compare data of newer studies with data of older studies, it is important to account for the correct atlas system (Evans et al. 2012).

2.5 Statistical Parametric Mapping (SPM)

Over now more than a quarter of a century, the freely available software package from the Wellcome Department of Cognitive Neurology, London, known as SPM (versions SPM'94 up to SPM'99, and SPM2 up to SPM12, which are all based on SPM'94 and use MATLAB (The MathWorks, Inc.) functions and subroutines), has helped in the standardization of measurement and data analysis in functional neuroimaging comprising analysis of fMRI, PET, SPET, EEG, and MEG data. Generally, its idea is based on the region-of-interest (ROI) technique with the difference that the regions-of-interest are now voxels in a standardized stereotaxic room. This software not only spatially normalizes PET, SPET, or fMRI images to the standardized stereotaxic Talairach and Tournoux atlas (Talairach and Tournoux 1988), but it can also perform statistical analyses on study groups on a voxel-by-voxel basis (Friston et al. 1991, 1995); this allows for reliable and objective image handling that could improve interstudy variability due to the analytical process itself. An example of SPM used in PET taken from Otte (2001a) is given in Fig. 2.8.

The various versions of SPM and a detailed description of the procedure can be retrieved from the following internet homepage for free: http://www.fil.ion.ucl.ac.uk/spm/.

This method is described in detail under the aforementioned link. In brief, after interfile conversion of the reconstructed transaxial brain files into an SPM-readable

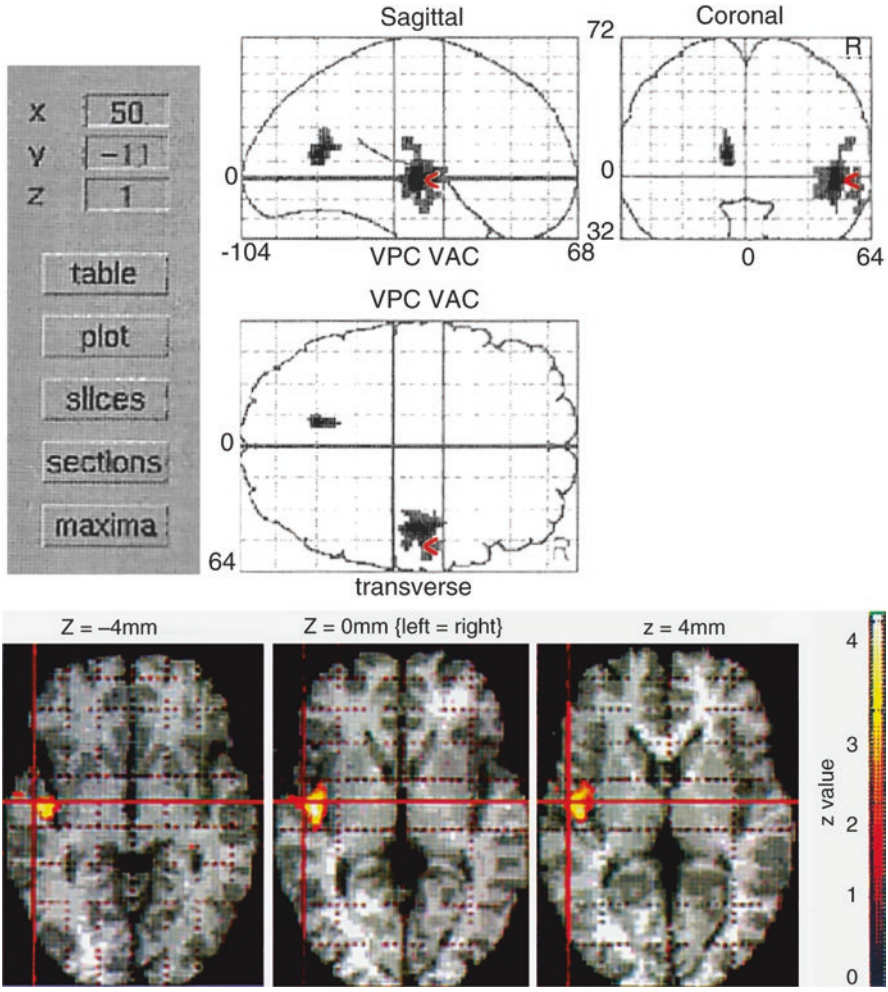

Fig. 2.8 Example of statistical parametric mapping (SPM) used in PET. (Adapted from Otte (2001b))

file format (e.g., ANALYZE format in SPM'94), images are transformed to the stereotaxic coordinate system of Talairach and Tournoux using SPM. Then, the normalized images of patients and healthy subjects are compared by computing a voxel-by-voxel *t*-statistic. The *t*-statistic is transformed to a normal statistic yielding a *Z* score for each voxel. Voxels exceeding the significance level, either indicating hypoperfusion/hypometabolism (deactivation) or hyperperfusion/hypermetabolism (activation) of a certain brain region, are then displayed in a "glass view" of transverse, sagittal, and coronal projections of a statistical parametric mapping.

2.6 Control Group

Any quantitative image analysis in functional neuroimaging is based on interindividual comparisons of data from a single patient or a patient group with data from a (normal) control group (Otte 2000). This applies to both the ROI analysis and the SPM method (Friston et al. 1991, 1995).

The recruitment of healthy volunteers is rather easy in some countries, but in many European countries it is difficult, as most ethical committees do not allow studies with exposition of radioactivity to healthy volunteers without any indication. If they do so, then it is only under strict regulation. Besides, the payment and offering of incentives to healthy volunteers have become contentious issues today.

Many institutions try to resolve this challenge by allowing for data from patients without brain alterations on previous scans or from oncological cases outside the brain having an additional ("normal") brain scan without the need for a further radioactive injection. However, especially in functional neuroimaging, this can cause potential pitfalls: First, such additional scans often follow other methodological protocols as compared with standardized brain scans; second, oncological patients may have brain alterations (e.g., Tashiro et al. 2000). Taking such oncological patients as a "normal control group" is, therefore, dangerous and may cause conflicting challenges in the evaluation of brain lesions not only in patients who are involved in compensation cases.

It is, of course, permissible to choose a group of patients with a known brain disease as a differential diagnostic control group. Furthermore, it is important to match the control group in age and gender and to perform a substantiated statistical power calculation for the number of control subjects needed.

Hence, caution is required, since the control group plays the most important but, at the same time, the most sensitive and vulnerable role in the quantitation of functional neuroimaging.

We will encounter this problem in some of the functional neuroimaging studies in whiplash injury (see Sect. 3.2).

2.7 Artificial Intelligence

Deep learning by artificial intelligence (AI) is currently finding its way into multiple healthcare applications (Topol 2019; Mouridsen and Borra 2021). It has also made its way into radiological imaging and has been successful in analyzing images for certain indications (e.g., Berthon et al. 2017; Huang et al. 2018; Hwang et al. 2019; Lu et al. 2018; Yang et al. 2015).

However, as we think, it cannot and should not replace the physician and his or her experience. It therefore remains to be assessed at the present time to what extent AI can be usefully employed in the automatic evaluation of brain PET or SPET data, particularly for the indication of whiplash—in our eyes, a very vulnerable area for the analysis of image data.

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Current Research Data

3

3.1 Mild Traumatic Brain Injury

3.1.1 General Aspects

Traumatic brain injury is usually assessed with the Glasgow Coma Scale (GCS), CT, and EEG. However, also a considerable number of articles with functional neuroimaging can be retrieved on mild traumatic brain injury. Many of these document that in mild traumatic brain injury, SPET and PET imaging are superior to the morphologically oriented procedures—like CT or MRI—as SPET or PET can also image functionally altered cerebral regions. Often, these functional lesions are larger and more frequent than in the CT finding.

Jacobs et al. (1994) designed a study to answer the question of whether the aforementioned superiority of functional imaging was also relevant: They found that perfusion SPET has a high negative-predictive value for the clinical outcome. It was shown that with initial negative SPET findings, 97% of the patients did not have any clinical symptoms 3 months after a mild-to-moderate brain damage, while 95% with clinical symptoms 3 months after the accident had a positive initial SPET scan. These results are very important in terms of rehabilitation and for the evaluation of the ability of the patient to work.

In the study from Ichise et al. (1994), patients with chronic symptoms after traumatic brain injury were investigated utilizing perfusion SPET compared to neuropsychological testing. The presence of pathological SPET findings correlated with a set of neuropsychological tests. Especially, it was found that by the determination of the ratio of anterior to posterior brain perfusion, the degrees of the morphological deficits could be predicted. By contrast, the ventricle to cortex ratio correlated only weakly with the neuropsychological tests.

Compared to the work of Ichise and colleagues, a study on survivors of severe closed head injury from Goldenberg et al. (1992) revealed a far worse correlation of SPET with the neuropsychological tests. In this context, it should be noted that a

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normal SPET or PET does not necessarily have to exclude mild traumatic brain lesions, as a diffuse axonal damage to the brain cannot be imaged by these imaging modalities.

In a combined ^{57}Co-/^{99m}Tc-HMPAO study, Audenaert et al. (2003) could show that ^{57}Co-SPET is able to outline the site and extent of brain damage in patients with mild traumatic brain injury, even in the absence of structural lesions and that it may confirm and localize findings from neuropsychological testing.

Goethals et al. (2004) studied the neural basis associated with performance on the Stroop Colored-Word test interference subtask in patients with diffuse brain injury using SPM and SPET. They could show that patients with diffuse brain injury were slower than healthy controls on the interference subtask of the Stroop test associated with activation effects in posterior (mainly parietal) brain areas in addition to activation of anterior (mainly anterior cingulate) brain regions.

3.1.2 Special Cases

The number of single cases and tragedies resulting from traumatic brain injuries is dramatic and could fill many books. We would, therefore, like to show some exemplary cases (data from Otte and Brändli (1998) and Otte et al. (1998b)).

3.1.2.1 Bicycle Accident

In this case, a 35-year-old man was referred to hospital after a bicycle accident where he had hit the right side of his head on the street. On the day of the accident, he complained of cervical pain, extraordinary right-hemispheric headache, dizziness, fluctuating vertigo, and visual symptoms (oscillopsia). Neuropsychological testing exhibited a marked reduction of attention and concentration for tonic and phasic alertness, for divided attention, and for the cognitive information processing speed. In addition, verbal and visuospatial memory was reduced. CT and MRI showed no pathological findings of the brain. The EEG revealed right-hemispheric general changes in the temporoparietal brain region. Using FDG-PET and SPM, a marked reduction of glucose utilization in the right frontal, parietal, and occipital region could be detected (Fig. 3.1).

One year after the accident, the patient had to give up his job due to persisting deficits in concentration, memory, and attention; he also had to stop his studies at university which he had started alongside his job. The headache, the visual symptoms, and the fluctuating vertigo attacks persisted.

Bicycle accidents can cause many kinds of injuries; the serious ones are mainly resulting from head impact (Thompson et al. 1989). Those patients with head injuries and negative brain CT or MRI, but persisting cerebral dysfunctions, are often judged to be malingerers despite the fact that quantitative functional neuroimaging, such as PET or SPET, demonstrates brain dysfunctions, as in the reported case.

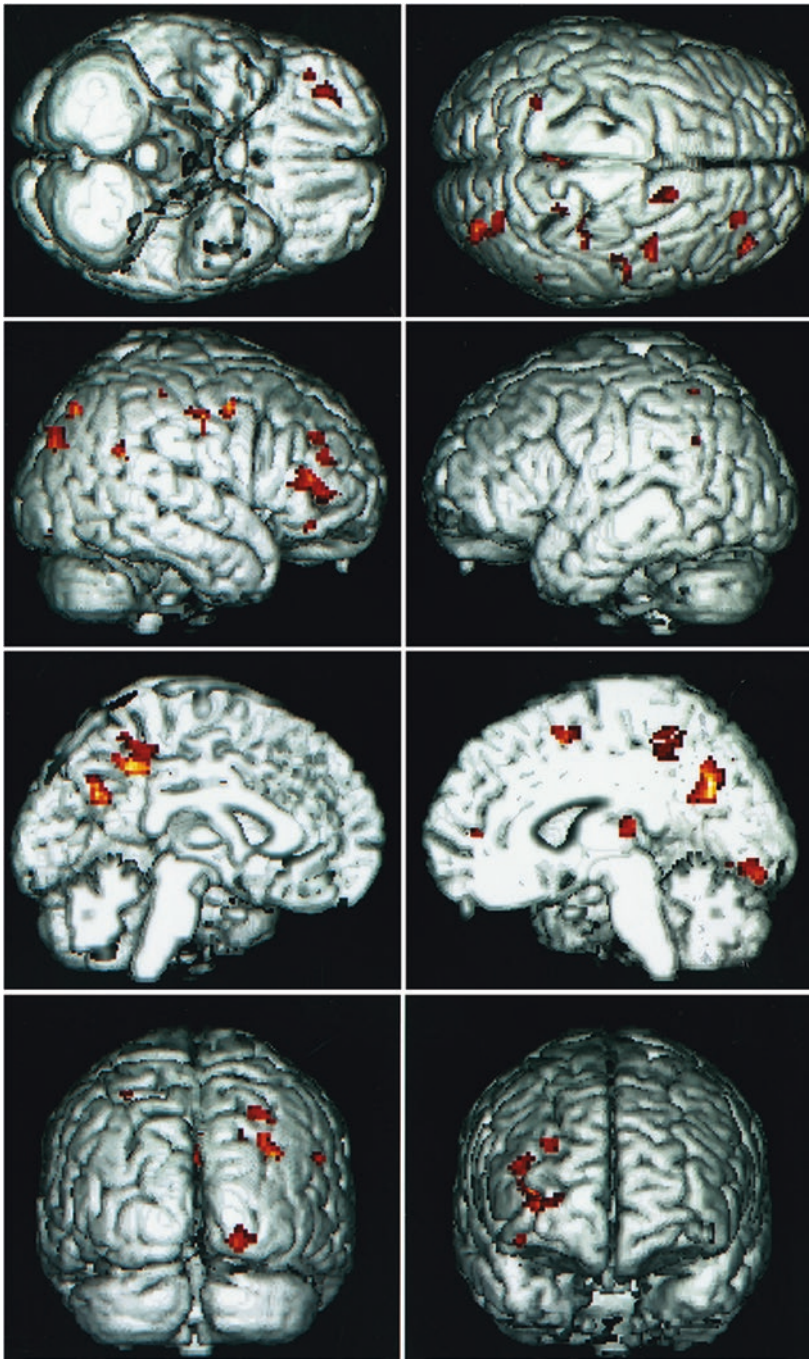


Fig. 3.1 FDG-PET SPM image of a patient after bicycle accident showing a marked reduction of glucose utilization in the right frontal, parietal, and occipital region of the brain. (This figure was published in Otte et al. (1998b), copyright Elsevier (1998). With kind reproduction permission from Elsevier Ltd.)

3.1.2.2 Car Accident

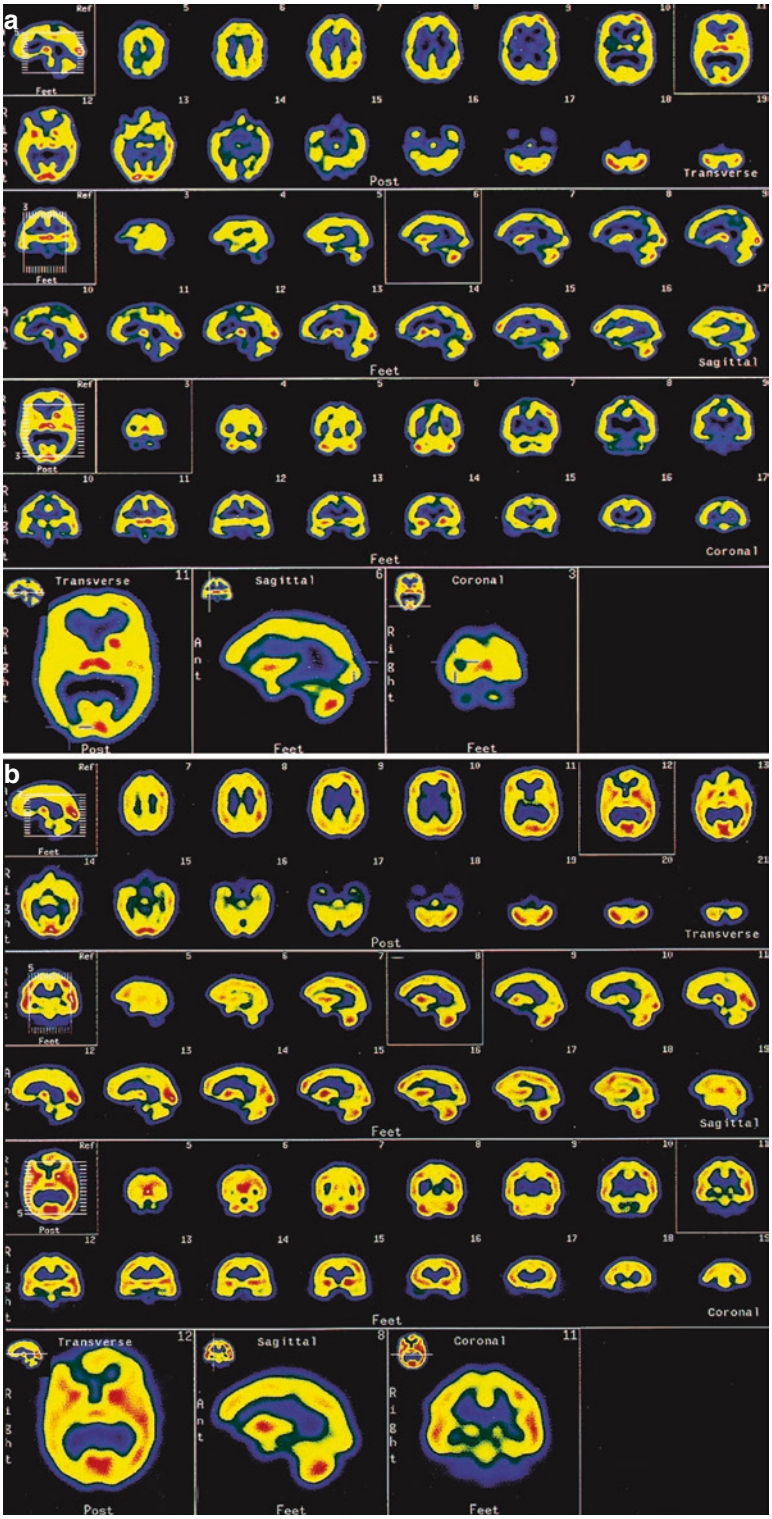
A 47-year-old woman had a mild traumatic brain injury as a consequence of a rear-end car collision and subsequently developed a posttraumatic distress syndrome with changes of her personality and depression. She complained about mood changes, alterations in concentration and memory, sleep disturbances, occipital headache, vertigo, fluctuating visual disturbances, tendency toward aggressiveness, and fatigue.

The clinical investigation revealed a lateralization of Weber's test to the left ear from where it had bled after the accident. Furthermore, the patient had hyposmia at the right side for aromatic and trigeminal irritants. She also had a tender point at the third cervical spine and pain of the shoulders and neck. ^{99m}Tc-ECD (Neurolite) SPET 20 months after the accident showed hypoperfusion in the right posterior parietal occipital and in the right frontobasal regions (Fig. 3.2a).

In a follow-up investigation 44 months after the accident, an improvement of the patient's cervical, neck, and shoulder pain and a disappearance of the fluctuating visual disturbances and occipital headaches were observed. Tests for memory and concentration were normal. By contrast, her tendency toward aggressiveness did not change, and the hyposmia at the right side turned into anosmia. The follow-up ECD-SPET scan revealed a normal perfusion in the right posterior parietal occipital region, but a clear accentuation of the right frontobasal hypoperfusion (Fig. 3.2b).

In this case, brain perfusion is correlated with the patient's clinical symptoms. Hypoperfusion of the posterior parietal occipital region that is localized to the watershed zone between the territories of the larger cerebral arteries may be the substrate of the cognitive and visual disturbances in the reported patient, as the parietal and occipital regions have functions in the maintenance of attention and in complex sensory processing (Mesulam 1985). Frontal lesions are well known to cause changes in personality, as well as frontobasal lesions are related with hyposmia or anosmia. In the reported case, the lesions in the frontobasal and posterior parietal occipital region at the right side can be explained by brain contusions as a consequence of a coup-contrecoup mechanism. Interestingly, the posterior parietal occipital lesion disappears, whereas the frontobasal defect accentuates. This emphasizes both the plasticity and the susceptibility of the brain to contusion mechanisms.

Fig. 3.2 Perfusion SPET (^{99m}Tc-ECD [Neurolite]) in a patient with car accident and mild traumatic brain injury: (**a**) 20 months after the accident showing hypoperfusion in the right posterior parietal occipital and right frontobasal region and (**b**) 44 months after the accident showing a normal perfusion in the right posterior parietal occipital region, but a clear accentuation of the right frontobasal hypoperfusion. (These figures were published in Otte and Brändli (1998), copyright Elsevier (1998). With kind reproduction permission from Elsevier Ltd.)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3.2 Whiplash Injury

In comparison to literature data on mild traumatic brain injury, the bibliography on whiplash injury and late whiplash injury is slightly smaller, albeit persistently increasing over the last few years. This may also result from the practice that sometimes studies of whiplash injury are entitled studies of mild traumatic brain injury. Still, PET or SPET data in whiplash brain are rare, however, and currently only available mainly from data of a small number of research groups.

3.2.1 Early Studies from Otte et al.

Over many years, Otte et al. (1995a, b, 1996a, b, 1997a, b, c, d, 1998a) and Otte (1998, 1999, 2000a, d, 2001a, b, c) have performed several studies with SPET and PET using different tracers (^{99m}Tc-labeled HMPAO, ^{99m}Tc-labeled ECD, and ^{18}F-labeled FDG). In these studies, altogether over 500 patients with late whiplash syndrome were investigated at rest. With many of these patients, a—compared to a healthy control group—statistically significant relative reduction of the tracer in the posterior parietal occipital region, mostly affecting both sides, was seen (Fig. 3.3). These studies were preponderantly without a voxel-based analysis (SPM), and the ROI technique or (in the very early studies) a visual analysis were the standard approaches.

The aforementioned finding of hypoperfusion/hypometabolism in the posterior parietal occipital region could be reproduced by utilization of different SPET systems (dual-headed, triple-headed camera), different filter systems, different tracers (HMPAO, ECD, and FDG), and different kinds of image interpretation such as visual analysis, semiquantitative ROI technique, and the observer-independent SPM procedure (Otte et al. 1995a, b, 1996a, b, 1997a, b, c, d, 1998a; Otte 1998, 1999, 2000a, b, c, d, 2001a, b, c).

In addition, in individual cases, there was a tracer reduction in regions apart from the posterior parietal occipital region, e.g., in the frontal and/or temporal lobe. These changes were, however, not group-specifically significant, i.e., the whiplash patient group did not have the common characteristic of a perfusion reduction in the frontal or temporal region; however, an individual patient compared to a control group could have statistically significant perfusion reductions in these regions.

Some neuroimaging SPET examples of patients with late whiplash syndrome are presented in Figs. 3.4 and 3.5.

In a study from 1997 (Otte et al. 1997b), 6 whiplash patients as well as 12 normal controls were examined both by SPET (perfusion tracer ^{99m}Tc-ECD) and PET (glucose metabolism tracer ^{18}F-FDG). Standardized elliptical regions of interest were placed in various *Talairach*-standardized transaxial slices in different brain regions and normalized to the perfusion and glucose utilization in height of the basal ganglia (resulting in the perfusion index and glucose metabolic index). In both assessments, a statistically significant and matching decrease in perfusion/metabolism was found in the posterior parietal occipital region of both brain sides. This decrease

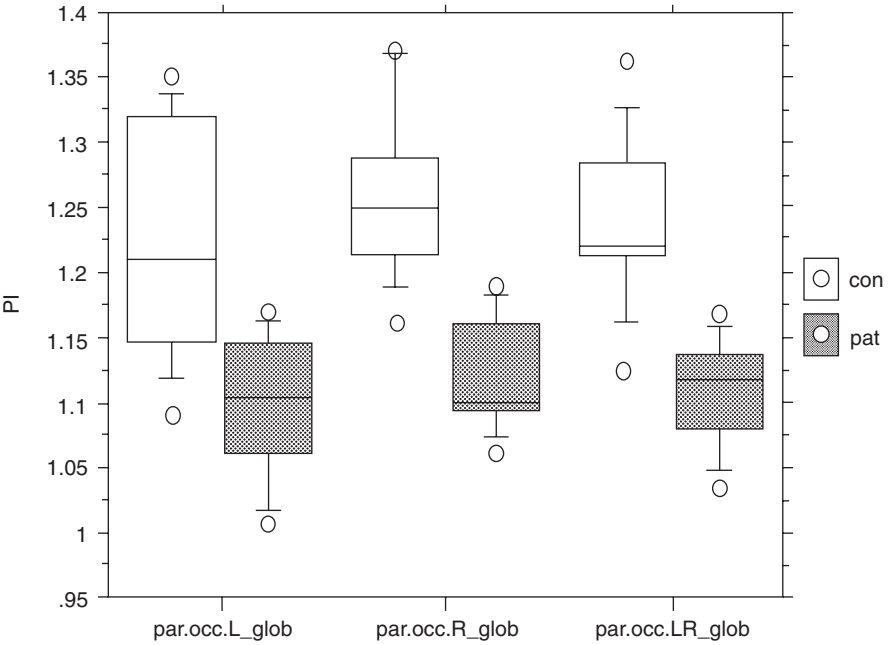

Fig. 3.3 Box plot of the perfusion indices in the posterior parietal occipital region related to the global perfusion at height of basal ganglia determined by perfusion SPET (^{99m}Tc-ECD) and region-of-interest technique. Ten patients with late whiplash syndrome are compared to 11 controls. par.occ.L_glob means the perfusion index for the posterior parietal occipital region related to global for the left side, par.occ.R_glob for the right side, and par.occ.LR_glob for the means of both sides: con = control group, pat = patient group. The investigation resulted in statistically significant differences between the patient and the control group (Mann–Whitney *U*-test) (par.occ.L_glob con-pat: $p = 0.0031$; par.occ.R_glob con-pat: $p = 0.0002$; and par.occ.LR_glob: $p = 0.0003$). (Originally from Otte et al. (1996a), adapted from Otte (2001d))

was group specific; in individual cases, also other regions of significantly decreased perfusion/metabolism were observed, such as in the frontal, parietal, and temporal lobe or in the brain stem. However, there were no statistically significant group differences in these additional brain regions (Figs. 3.6 and 3.7).

It was hypothesized that the hypometabolism in the posterior parietal occipital region is caused by activation of nociceptive afferents from the upper cervical spine. This hypothesis is based on a study by Moskowitz and Buzzi (1991) from which it is known that irritation of nociceptive afferents of the projections of the trigeminal nerve has different effects on local vasoactive peptides and the cranial blood vessel system (Fig. 3.8). The fact that the posterior brain perfusion area, in particular the area of the terminal vascular bed between the A. cerebri media and the A. cerebri posterior (which is primarily the posterior parietal occipital region) is mainly affected, can be explained by the knowledge that this area is attributed one of the most vulnerable regions of the brain (Graham and Brierly 1984; Otte 2000d, 2019) (Fig. 3.9).

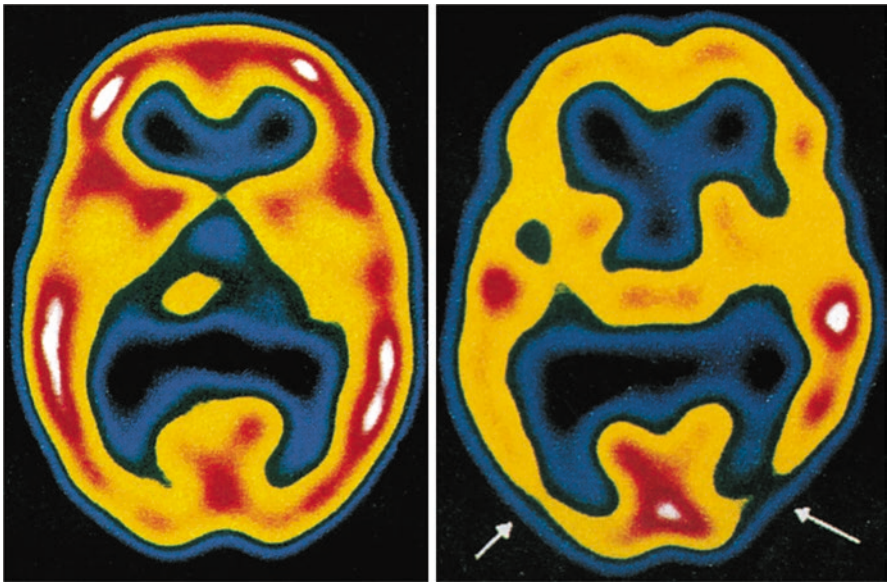

Fig. 3.4 Late whiplash syndrome, example 1: *Left*: Normal control and *right*: whiplash patient with persisting symptoms 2 years after accident. Representative transaxial slices at level of basal ganglia: perfusion SPET. A perfusion reduction can be seen on both sides of the posterior parietal occipital region, see *arrows*. (This figure was published in Otte et al. (1997a), copyright Elsevier (1997). With kind reproduction permission from Elsevier Ltd.)

To test the hypothesis of nociceptive afferences versus contusion mechanism, Otte et al. (1998c) reevaluated their large group of whiplash patients scanned with ^{99m}Tc-ECD SPET and found 15 patients who themselves drove their cars and who all could remember that they looked to the right side when the rear-end car collision happened. Ten of the 15 patients reported that they had hit their heads on the steering wheel, and the other five could not remember. Otte et al. checked these 15 patients against 15 age- and sex-matched healthy volunteers using SPM96.

The whiplash patients revealed a significant hypoperfusion in the posterior parietal occipital region of both hemispheres and in the left frontal region (Fig. 3.5).

As the patients looked to the right side during the accident, a contusion mechanism could be discussed for the left frontal and the right posterior parietal occipital region, regardless if this was produced directly by hitting the head to the steering wheel or by the acceleration forces producing indirect head impact. If whiplash injury only was a form of mild head injury with a contusion mechanism, the additional left posterior parietal occipital hypoperfusion in the above patients could not be explained. Therefore, the authors conclude that posterior parietal occipital hypoperfusion in whiplash patients may still be hypothesized to be elicited from lesions of neuroceptive afferents from the upper cervical spine. Of course, this does not exclude, so the authors, that brain contusions must carefully be evaluated, as additional contusion is well known to have an effect on clinical outcome after injury. In

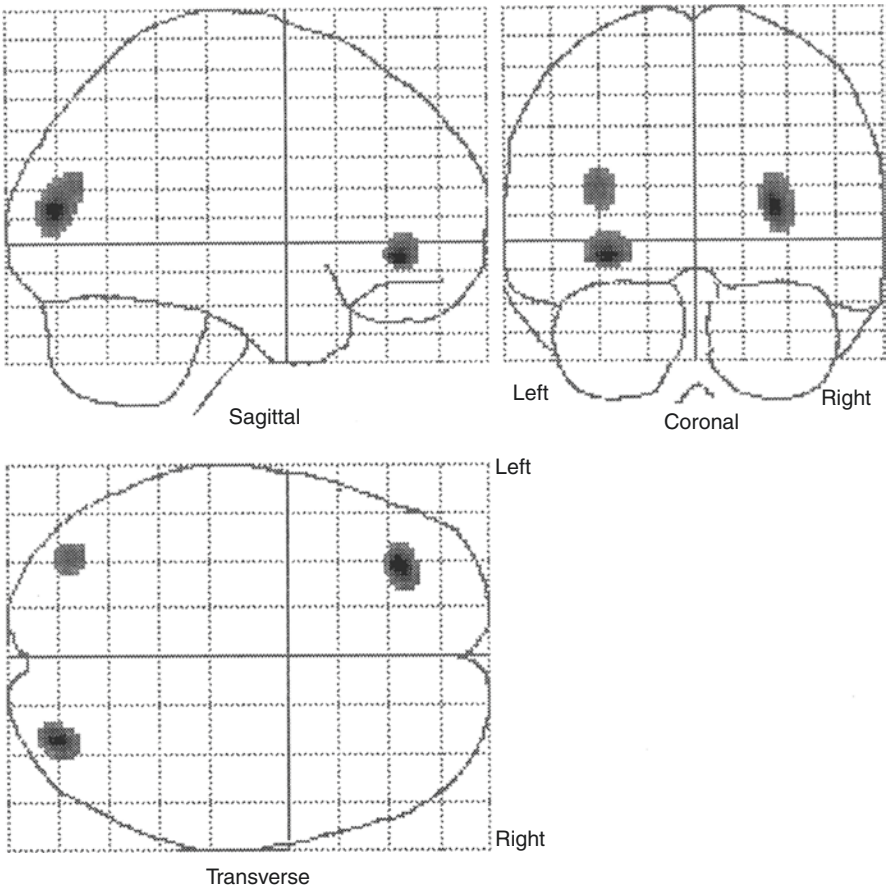

Fig. 3.5 Late whiplash syndrome, example 2: Statistical parametric map projections; brain areas with significantly decreased relative perfusion (level of significance: $p < 0.01$) of 15 whiplash patients compared to 15 healthy controls are shown; from these 15 whiplash patients, all could remember that they had looked to the right during the impact; 10 patients reported that they had hit their heads at the steering wheel. Statistically significant differences are displayed on sagittal, coronal, and transaxial projections of the brain: ^{99m}Tc-ECD-SPET. Note the hypoperfusion in the posterior parietal occipital region at both sides and in the frontal region on the left side; the hypoperfusion frontal left—posterior parietal occipital right—may be explained by a traumatic coup-contrecoup mechanism, whereas the additional hypoperfusion in the posterior parietal occipital region on the left side can only be explained by the additional whiplash injury. (Originally from Otte et al. (1998a), adapted from Otte et al. (eds) (2004) Nuclear Medicine in Psychiatry, Springer, Heidelberg)

addition, in head injury, the typical contusion regions of postmortem brains have been investigated already in 50 cases of people dying from head injury by Courville (1937). These are shown in Fig. 3.10, and it can be seen that the posterior parietal occipital region is not a usual anatomical contusion localization in traumatic brain injury. By contrast, while SPET findings after traumatic brain injury also

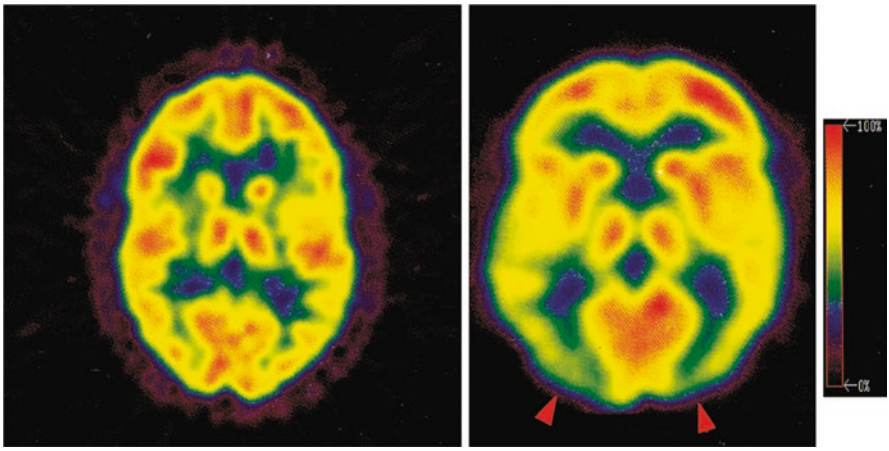

Fig. 3.6 FDG-PET; representative transaxial slice in height of basal ganglia, *left*: normal control subject, *right*: whiplash patient; *arrows* indicate hypometabolism in the posterior parietal occipital region (data from Otte et al. (1997b), adapted from Otte et al. (eds) (2004) Nuclear Medicine in Psychiatry, Springer, Heidelberg)

accumulate frontally and temporally, several authors found even more diffuse bilateral perfusion reductions in the posterior parietal occipital region (Britton et al. 1991; Jacobs et al. 1994; Masdeu et al. 1995), which, according to the pathological-anatomical knowledge, are not where contusions are to be expected. Britton et al. (1991) hypothesized that these are ischemic zones, as shown by Graham et al. (1978), in fatal severe traumatic brain injury with intracranial pressure and hypotension. However, lesions in the posterior parietal occipital region are also found in mild cranio-cerebral traumas (Jacobs et al. 1994; Masdeu et al. 1995) and more commonly in whiplash injuries.

3.2.2 Studies from Bicik/Radanov et al.

In a study with FDG-PET, HMPAO-SPET, and MRI, Bicik et al. (1998) examined a small sample size of 13 patients with "typical whiplash syndrome." They compared the PET and SPET data, however not the MRI data, with 16 controls. The controls comprised four healthy students and 12 melanoma patients.

The group found by SPM a significantly decreased metabolism in the frontopolar, temporolateral region, as well as in the putamen. The frontopolar changes correlated significantly with the Beck Depression Inventory scale. In the posterior parietal occipital region, a decreased perfusion and glucose utilization was found, but this hypometabolism correlated with a cortical thinning in the MRI. Based on their small sample size, the group concluded that the FDG-PET or HMPAO-SPET was not recommendable as diagnostic routine investigation for whiplash patients.

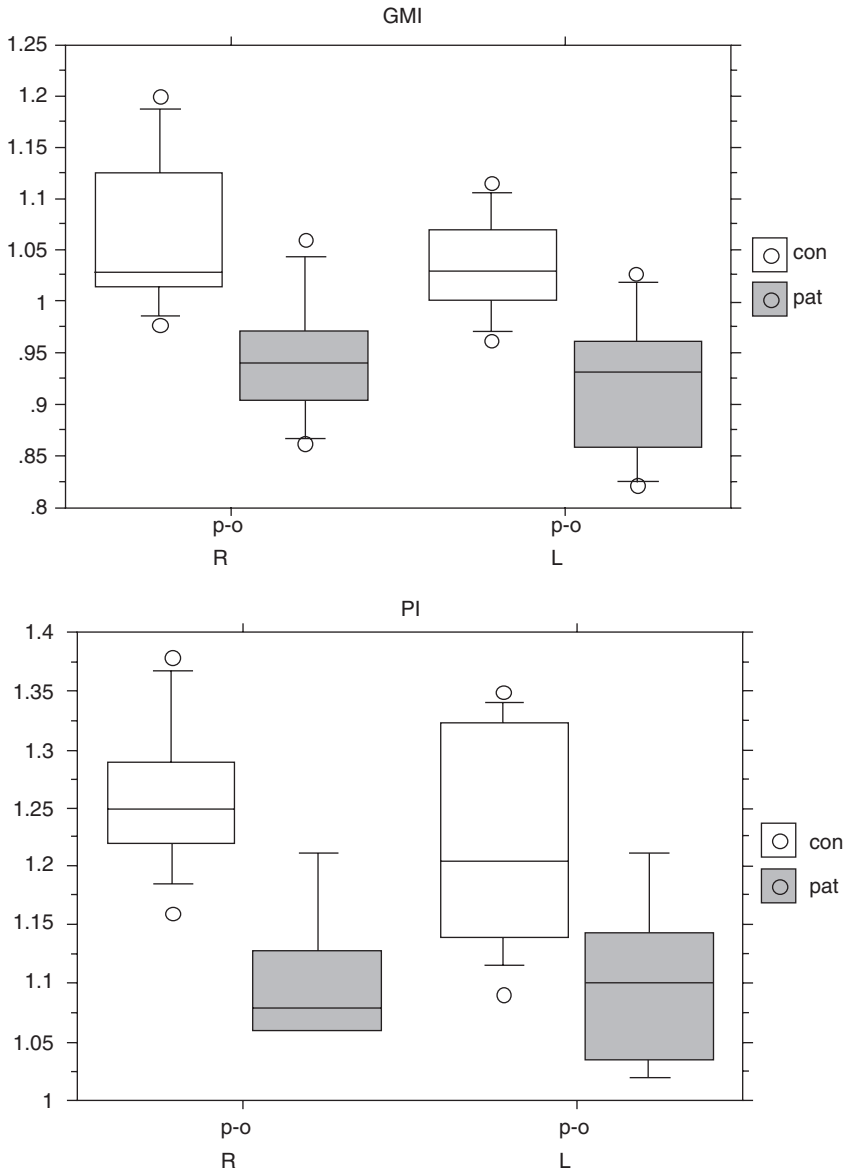

Fig. 3.7 *Above*: box plot of the glucose metabolic indices (GMI) determined by ^{18}F-FDG-PET and region-of-interest technique in the posterior parietal occipital region related to the global glucose metabolism at height of the basal ganglia. *Below*: box plot of the perfusion indices (PI) determined by ^{99m}Tc-ECD. Six whiplash patients were compared with 12 controls in both assessments. p-o L means posterior parietal occipital region left, and p-o R, posterior parietal occipital region right: con = control group, pat = patient group. The investigation resulted in statistically significant differences between the patient and the control group both in the GMI and the PI values (Mann–Whitney *U*-test) (GMI: p-o R con-pat: $p = 0.0092$, p-o L con-pat: $p = 0.0067$; PI: p-o R con-pat: $p = 0.0039$, p-o L con-pat: $p = 0.0273$). (Data from Otte et al. (1997b), adapted from Otte et al. (eds) (2004) Nuclear Medicine in Psychiatry, Springer, Heidelberg)

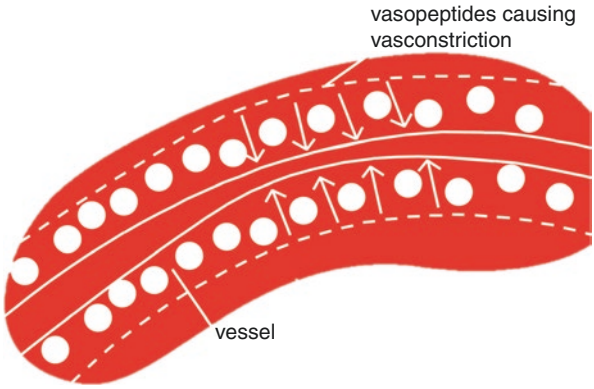

Fig. 3.8 Scheme of the nociceptive-vascular hypothesis in whiplash syndrome based on Moskowitz and Buzzi 1991: It is assumed that the nociceptive afferents ascending from the upper cervical spine trigger an increased vasopeptide production in the vessels. This results in vasoconstriction of the vessel

This study was discussed in one of the later issues of the journal where it was published with a reply by one of the authors representatively for the working group (Otte 1999; Buck 1999). In this scientific discussion, it was pointed out that the control group consisted mainly of melanoma patients, a group of patients, thus, who exhibit neuropsychological changes high-probably alone due to emotion-related cognitive changes based on the awareness of their cancer illness. A neuropsychological testing to exclude any bias with this was, unfortunately, not performed for this so-called "control" group. Moreover, in a study from Tashiro et al. (2000), SPM and FDG-PET impressively revealed statistically significant brain alterations (mainly in the frontal and parietal regions) in oncological patients (see also Sect. 2.5).

Furthermore, the study by Bicik et al. did not perform an MRI of the brains of the control group. Exactly, this is, however, the main weak point of the study: It would have been of utmost interest to compare the cortical thickness to the brain perfusion also in the control group. This would have helped to find out if the cortical thickness in the posterior parietal occipital region, which in the patient group did correlate with the decreased perfusion, was equal or not equal between controls and patients. Hence, the key question of whether the posterior parietal occipital region is functionally or morphologically "thinned" in whiplash patients remains unanswered in this study.

The study group of the article from Radanov et al. (1999) consists of nearly the same members as the one by Bicik et al. The difference to the publication of Bicik et al. lies in the addition of neuropsychological testing to the functional neuroimaging PET and SPET. Radanov et al. found that whiplash patients have positive findings in neuropsychological tests for cognitive functions, but no significant correlation between the regional brain perfusion or the glucose utilization and the scores in the tests of divided attention or working memory. The authors conclude that in late whiplash syndrome, there is no correlation between diagnosable morphological or functional brain deficits and cognitive functions; they, therefore, surmise that the emotional and cognitive symptoms are triggered but not caused by the whiplash injury. Most of this, however, contradicts to the work by Ichise et al. (1994).

An editorial by Alexander (1998) states that a pure whiplash injury can cause a traumatic brain injury and that functional brain deficits can be measured subsequent

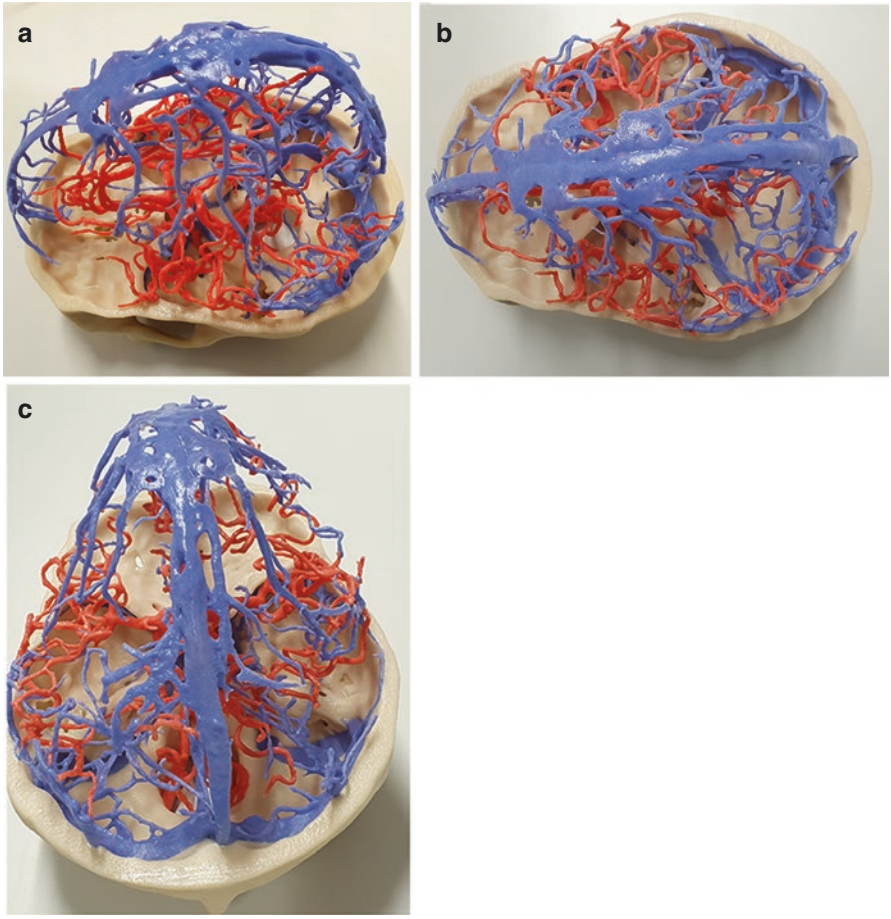

Fig. 3.9 3D print of the brain integrating angiographic data of the cranial arterial (shown in red) and venous system (shown in blue) into a single model (Erler-Zimmer, Lauf, Germany), photographs from different views: (**a**) from oblique lateral, left side: frontal, right side: occipital; (**b**) from cranial, left side: frontal, right side: occipital; (**c**) from occipital, below: occipital, above: frontal. There are some territories which are more vulnerable than other territories; these are located in so-called watershed regions at the boundary of the large cerebral arteries. The most vulnerable watershed region of the brain is between the Arteria cerebri media and the Arteria cerebri posterior. In this territory, the posterior parietal occipital region is located

to whiplash injury; however, Alexander is not in favor of the application of SPET, even if correlated to neuropsychological tests, for the verification of the cause of the brain lesion. Poeck (1999) states that the new functional imaging data are not recommendable for the diagnosis of the late whiplash syndrome. Both, Alexander and Poeck, base their argumentation on the study from Bicik et al., in which case, as we think, a critical approach to the interpretation of their comments should be taken (Otte 2000d).

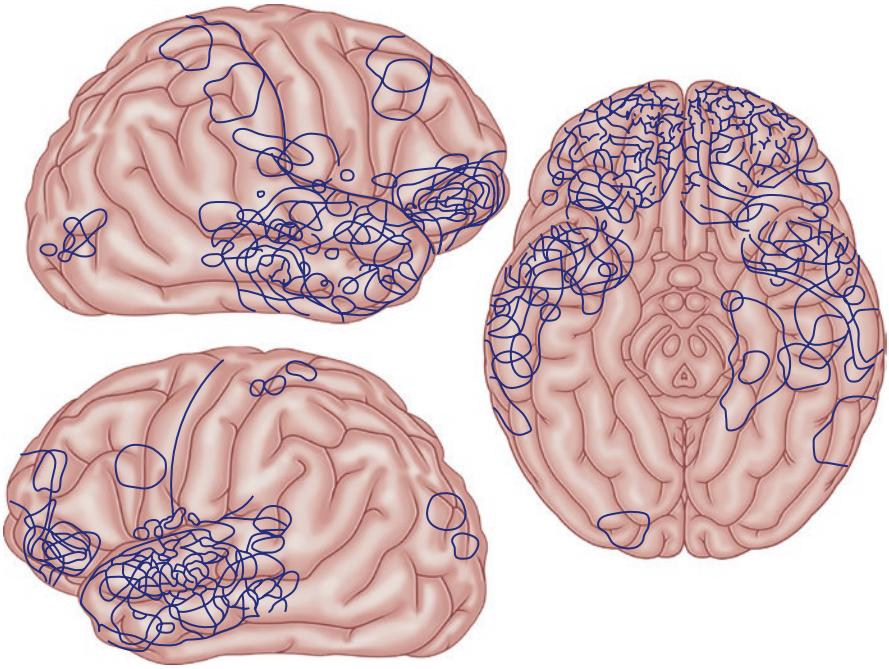

Fig. 3.10 Pathological-anatomical distribution of the postmortem localizations involved in brain contusion subsequent to closed head injury (adapted from Courville (1937); Courville had a large experience of the pathology of the central nervous system obtained in about 15,000 thousand autopsies; in this scheme the data are derived from 50 cases of people dying from head injury). The frontal and temporal regions are usually most frequently affected. The posterior parietal occipital region, which can be altered after whiplash injury, is not affected. For this, a different mechanism must be postulated (adapted from Otte (2001d))

3.2.3 Newer Studies from 2002 to 2012

By contrast to the above studies, in a recent study from Lorberboym et al. (2002), 20 patients with late whiplash syndrome were investigated with HMPAO-SPET and tests of perception and cognition including the P300 (an electrophysiological marker of cognitive ability), the digit span test, the word list generation test, two bedside memory tests, the Hamilton Depression Rating Scale, the Hamilton Anxiety Scale, and the Rivermead Postconcussion Symptoms questionnaire. A control group of nine volunteers without whiplash or head trauma was also tested. The authors found the following interesting results, which are also important for the validity of the aforementioned studies by Otte et al.:

- While no structural brain damage was seen in any patient on MRI, 13 of the 20 patients had brain perfusion abnormalities in one or more regions: Eight of these 13 patients had decreased perfusion in the temporal lobes, 3 patients had occipital perfusion abnormalities, 2 patients showed frontal lobe abnormalities, and 2 patients had asymmetric perfusion in the basal ganglia.

- Eight of 15 patients had abnormal P300 studies, and 7 of these 8 patients with abnormal P300 results had also an abnormal SPET study. From the 7 of 15 patients with normal P300 results, 6 had a normal SPET.
- Although there was no significant correlation between the SPET findings or the P300 results and the scores of attention and working memory, there was a close agreement between the SPET and P300 findings.

Data from larger patient collectives on the diagnostics of the late whiplash syndrome by using functional MRI or magnetic resonance spectroscopy to the best of our knowledge still do not exist, although they would certainly be desirable. However, we know of one encouraging pilot study in five symptomatic patients with late whiplash syndrome, five asymptomatic patients after whiplash trauma, and a control group of seven volunteers without the history of trauma; in this study, tests for visual motion perception and functional MRI measurements during visual motion stimulation were performed (Freitag et al. 2001). Symptomatic patients presented a significant reduction in their ability to perceive coherent visual motion compared to controls, whereas the asymptomatic patients did not show this effect; functional MRI activation was similar during random dot motion in all three groups, but was significantly decreased during coherent dot motion in the symptomatic patients compared with the other two groups. Reduced psychophysical motion performance and reduced functional MRI responses in symptomatic patients with late whiplash syndrome suggest a functional impairment in cortical areas sensitive to coherent motion. These findings in visual motion perception are in accordance with the SPET and PET findings in the posterior parietal occipital region and present a first and important proof of evidence of these cerebral findings by another imaging method.

In 2004, Lass and Lyczak reported about a patient aged 46 years who had a car accident with whiplash injury, without a loss of consciousness. This patient, so the authors, gradually developed cognitive impairment and was unable to come back to work. Whereas CT and MRT were normal, perfusion SPET showed significant hypoperfusion of the temporal and parietal lobes (Fig. 3.11).

Sundström et al. (2006) studied regional cerebral blood flow (rCBF) using ^{99m}Tc-HMPAO SPET and SPM'99 in 27 patients with chronic whiplash syndrome, 18 nontraumatic chronic neck pain patients, and 15 healthy controls. The nontraumatic neck pain patients had rCBF alterations as compared to the whiplash patients and the healthy control group, comprising hypoperfusion in the right temporal region near to the hippocampus and hyperperfusion in the left insula. Although the whiplash patients showed no significant differences in rCBF as compared to healthy controls, two nonsignificant small regional differences could be found, one in the right temporal and one in the left temporoparietal region, which were detected at an uncorrected voxel level of $p = 0.001$. The finding in the left temporoparietal region (representing the somatosensory area) matches our studies. The difference to our studies may be explained by the tracer used: Sundström et al. used ^{99m}Tc-HMPAO (Ceretec), whereas we mainly used ^{99m}Tc-labeled ECD (Neurolite) for SPET and, in later studies, ^{18}F-FDG for PET. In a study already from 1997, we could show that ECD more often shows functional changes in whiplash injury than HMPAO (Otte et al. 1997a), an observation which has been seen also in other indications for functional neuroimaging.

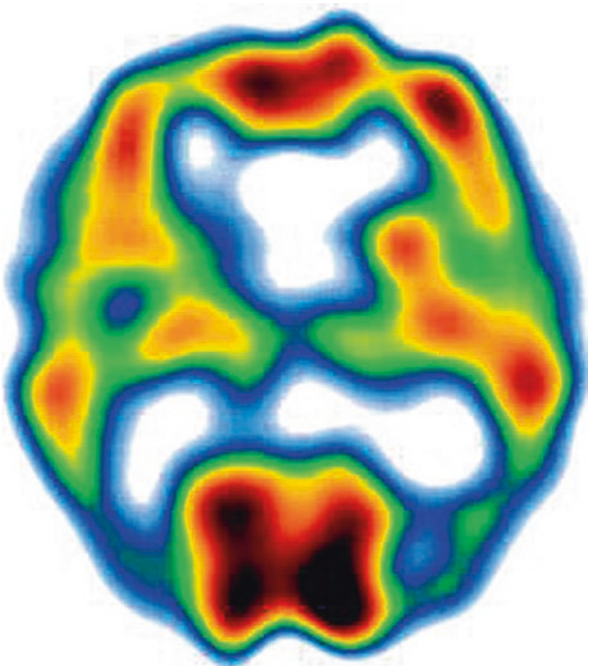

Fig. 3.11 Posterior type of hypoperfusion in a patient after whiplash injury. (This figure was published in Lass and Lyczak (2004), with kind permission from the *Hellenic Journal of Nuclear Medicine*, Thessaloniki)

Recently, Linnman et al. (2009) studied two objectives in whiplash injury:

1. To compare resting state rCBF by ^{15}O-labeled H_2O PET in 21 patients with whiplash-associated disorders (WAD) with 18 healthy, pain-free controls.
2. To investigate the relations between brain areas with altered rCBF to pain experience, somatic symptoms, posttraumatic stress symptoms, and personality traits in the patient group.

The group found elevated rCBF bilaterally in the posterior parahippocampal and the posterior cingulate gyri, in the right thalamus and the right medial prefrontal gyrus compared to healthy controls. Furthermore, they found lowered rCBF in the temporo-occipital regions compared to healthy controls.

These alterations in rCBF in the patients were correlated with neck disability ratings.

The authors concluded that there was an involvement of the posterior cingulate, parahippocampal, and medial prefrontal gyri in patients with WAD and speculated that changes in the resting state were linked to an increased self-relevant evaluation of pain and stress. Hyperperfusion in these areas was not systematically investigated in the past studies from Otte et al. (1995a, b, 1996a, b, 1997a, b, c, d, e, 1998a, b, c, d) and others. At that time only hypoperfusion was the focus of all studies due to the cognitive deficits reported in late whiplash syndrome.

Clas Linnman's reported relatively lower rCBF in the temporo-occipital areas is, however, consistent with the findings reported by Otte et al. (1995a, b, 1996a, b, 1997a, b, c, d, e, 1998a, b, c, d). Linnman and his coworkers state that these findings have also been observed in experimental models of pain. This is in accordance with the hypothesis from Otte et al. (1995a, b, 1996a, b, 1997a, b, c, d, e, 1998a, b, c, d) that neuroceptive afferents may be responsible for vasopeptide-induced vasoconstriction in the posterior parietal occipital regions (which is in the posterior watershed zone of the brain), as described by Moskowitz and Buzzi (1991) and Otte (2012).

Apart from rCBF, Linnman et al. (2010, 2012) have studied the substance P neurokinin-1 (NK1) receptor availability in patients with grade II whiplash-associated disorder using ^{11}C-GR205171 PET.

The group found reduced NK1 receptor availability in the ventromedial prefrontal, the insular and cingulate cortex, the hippocampus, the amygdala, and the periaqueductal gray area (Linnman et al. 2010).

In addition, Linnman et al. (2012) recently revisited their aforementioned (2010) data to investigate the brain NK1 receptor availability in the posterior parietal occipital region of whiplash patients and found a significantly reduced NK1 receptor availability in the left middle occipital gyrus, the right middle temporal gyrus, the left superior temporal gyrus, and the right superior temporal gyrus (Fig. 3.12).

These new data add further evidence to the original findings by Otte et al. in the posterior parietal occipital region of the brain after whiplash injury.

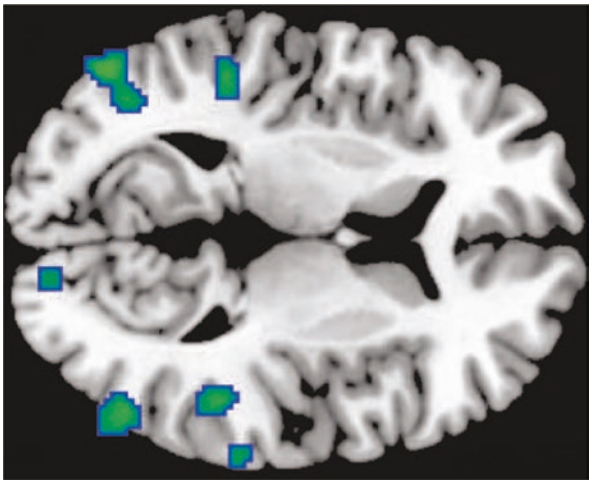

Fig. 3.12 Neurokinin-1 receptor availability imaged with ^{11}C-GR205171 PET in 18 patients with grade II whiplash-associated disorder compared to 18 healthy controls, region-of-interest analysis (statistical parametric mapping, SPM2) restricted to the temporal, occipital, and parietal lobe. The results are uncorrected for multiple comparisons and displayed on an MRI template at $p < 0.001$. (This figure is published in Linnman et al. (2012). With kind permission from Dr. Clas Linnman, P.A.I.N. Group, McLean Hospital, Harvard Medical School, U.S.A., and the *European Journal of Pain*, Elsevier Ltd. and John Wiley & Sons Ltd. (after the journal has transferred))

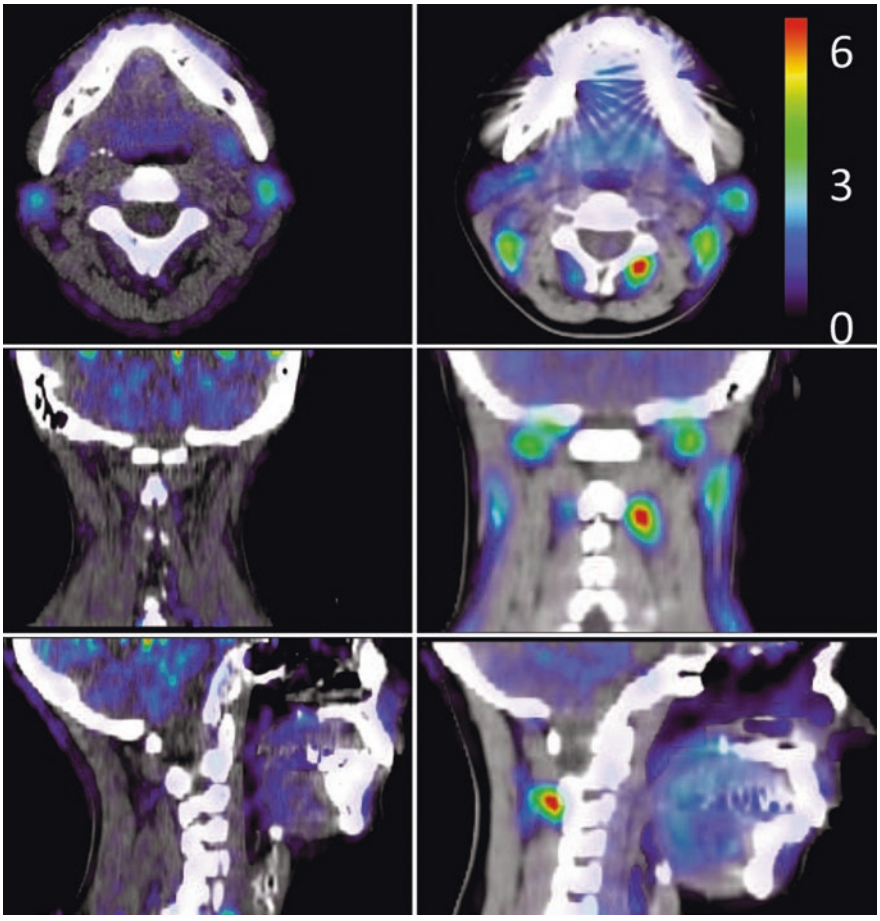

Fig. 3.13 ^{11}C-D deprenyl uptake in a representative healthy control (*left*) and in a patient with whiplash-associated disorders. ^{11}C-D deprenyl PET images are fusioned with the subject's individual CT scans. ^{11}C-D deprenyl uptake is expressed as standardized uptake value (SUV, see color bar in the figure). A high ^{11}C-D deprenyl uptake can be seen in the patient's adipose tissue preponderantly on the right side of the spinous process of the second cervical vertebra. (This figure was published in Linnman et al. (2011). With kind permission from Dr. Clas Linnman, P.A.I.N. Group, McLean Hospital, Harvard Medical School, U.S.A.; open-access license from *PlosOne*, www.plosone.org)

A further interesting study from Linnman and colleagues has been published (Linnman et al. 2011), which aims at investigating neck inflammation in patients with whiplash-associated disorders. In this PET study, the ^{11}C-labeled inflammation marker S-(+)-(d)-D-deprenyl is used. It could be shown that whiplash patients had a significantly increased ^{11}C-D-deprenyl uptake in the area surrounding the spinous process of the second cervical vertebra (Fig. 3.13), suggesting persistent musculoskeletal inflammation in this region. In 2021, the group from Clas Linnman

evaluated ^{11}C-D-deprenyl PET/CT images of the neck after acute whiplash injury in 16 adult patients (mean age 33 years) with whiplash grade II injury, and at 6 month follow-up (Aarnio et al. 2021). They found that whiplash injuries associated with experienced pain and disability can be visualized with ^{11}C-D-deprenyl PET/CT, since at 6 month follow-up one part of the patients had recovered, and one part had persistent symptoms—whereby reductions in ^{11}C-D-deprenyl uptake correlated with reductions in pain and disability.

A detailed German compendium on whiplash injury can be found in Graf et al. (2009), comprising a series of general aspects on anatomy, physiology, neurobiology, and psychology; on biomechanics; and on diagnostic and therapeutic approaches. In addition, a special focus of this book is on legal aspects and details in the German setting.

3.2.4 Latest Functional Neuroimaging Studies: Whiplash Revisited

One of the latest and, as we think, most pivotal functional neuroimaging studies in whiplash injury is the case–control study of Vállez García et al. (2016),[1] who investigated regional perfusion changes by ^{15}O-H_2O PET in 12 female patients with late whiplash syndrome compared to 8 healthy age-matched female volunteers in four different conditions (rest and different levels of non-painful electrical stimulation of the neck) and assessed several self-reported neurological tests in all participants (Hospital Anxiety and Depressive Scale, HADS; Visual Analogue Scale, VAS; Neck Disability Index, NDI; Whiplash Disability Questionnaire, WDQ). In the patient group, SPM (SPM12) revealed that perfusion was increased in the posterior cingulate and precuneus, and decreased in the superior temporal, parahippocampal and inferior gyri, the thalamus and the insular cortex (Figs. 3.14 and 3.15), and that there were no differences between the different levels of electrical stimulation.

Upon restricting the analysis to the parietal, occipital, and temporal lobes, small clusters of hypoperfusion were seen in the posterior parietal occipital region including some areas of hyperperfusion in this region (Figs. 3.15, 3.16, and 3.17, Tables 3.1 and 3.2).

Regarding the subjective neurological tests within the whiplash patient group, the average VAS was negatively correlated with the perfusion in the left frontal gyrus, the HADS was negatively correlated with the right precuneus, the NDI correlated positively with the right insula and negatively with the right precuneus, the WDQ score was positively correlated with the right precuneus, right insula, and right superior temporal gyrus, the perception threshold (of the electrical non-painful stimulation) was negatively correlated with the right superior temporal gyrus, and

[1] The full text of this open-access study including all supplementary material can be retrieved under https://www.ebiomedicine.com/article/S2352-3964(16)30313-9/fulltext

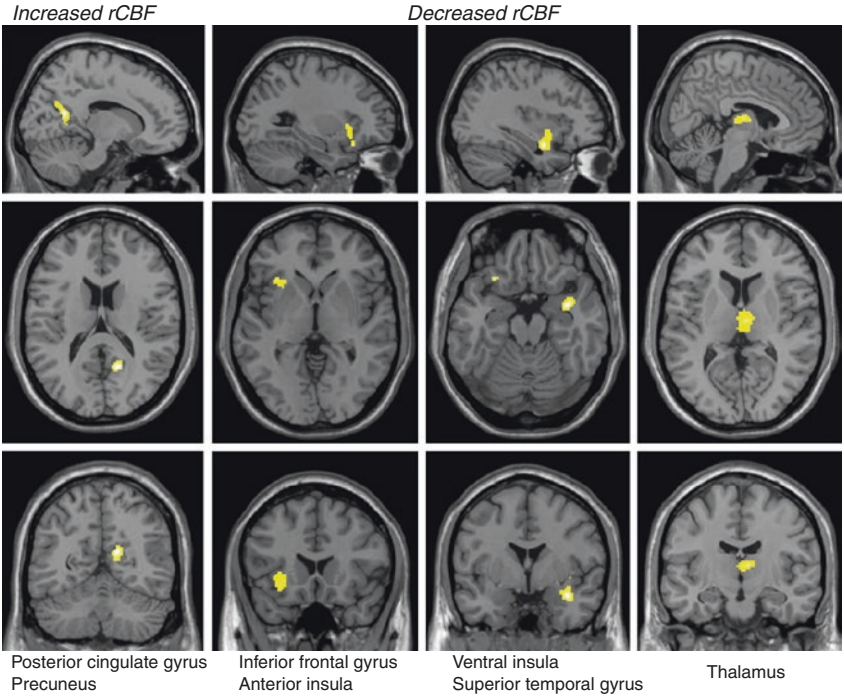

Fig. 3.14 Voxel-based analysis of $^{15}O\text{-}H_2O$ PET scans in the study from Vállez García et al. (2016), showing the significant regions of increased or decreased regional perfusion in patients with late whiplash syndrome as compared to healthy volunteers; height threshold $p = 0.005$ uncorrected, extent threshold $k = 100$ voxels, voxel size = 2 × 2 × 2 mm. (Copyright 2016 by Vállez García D, Doorduin J, Willemsen ATM, Dierckx RAJO, Otte A. DOI: https://doi.org/10.1016/j.ebiom.2016.07.008. Published by Elsevier B.V. under the open-access license CC BY NC ND [http://creativecommons.org/licenses/by-nc-nd/4.0])

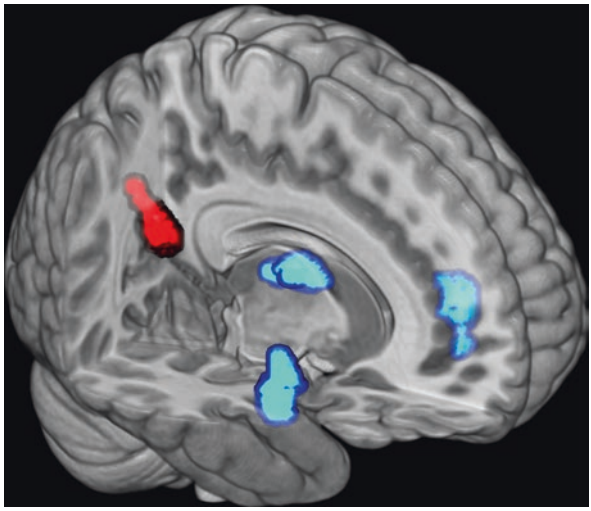

Fig. 3.15 MRIcron 3D visualization of the study from Vállez García et al. (2016) presented in Fig. 3.14, showing the significant regions of increased (red) or decreased (blue) regional perfusion in patients with late whiplash syndrome as compared to healthy volunteers. (Visualization by Dr. David Vállez García et al. (2016), with kind permission). MRIcron is an image viewer that can load multiple layers of images, generate volume renderings and draw volumes of interest

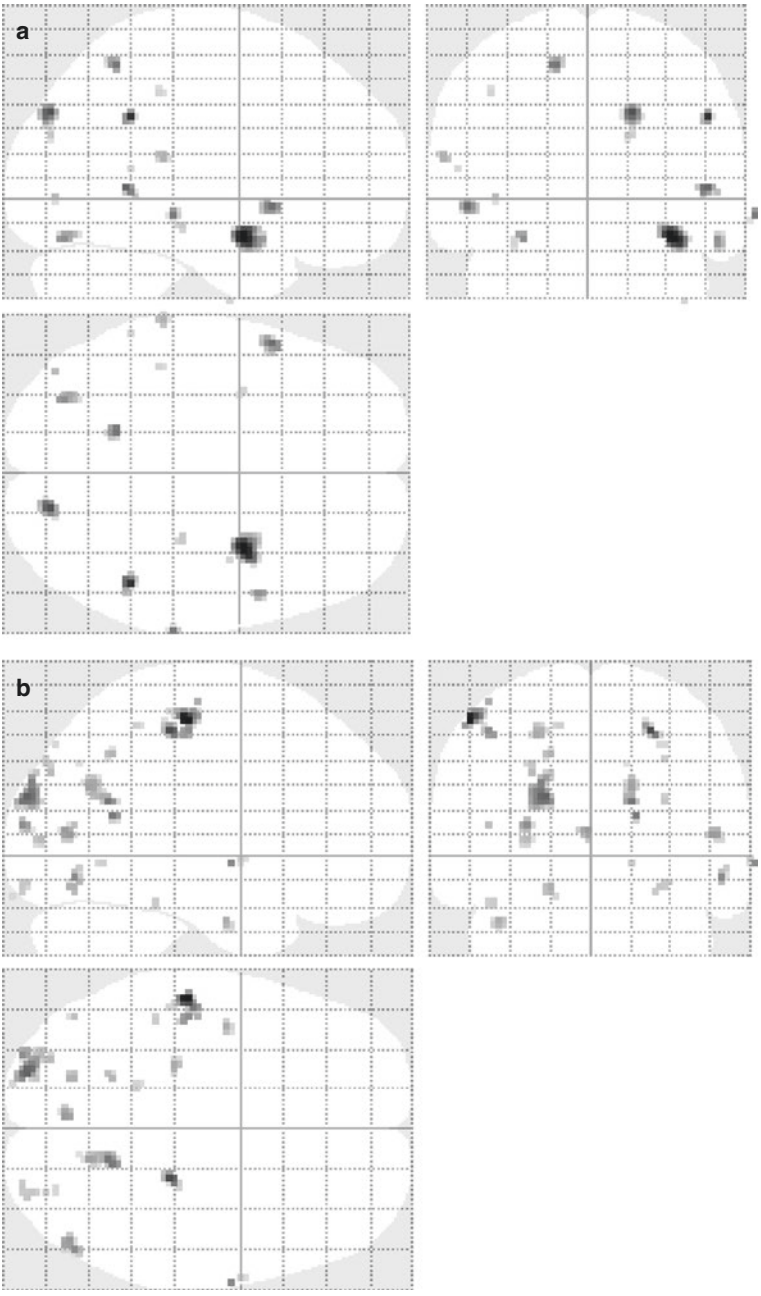

Fig. 3.16 Statistical parametric map projection showing (**a**) decreased regional and (**b**) increased cerebral blood flow in chronic whiplash-associated disorder patients as compared with healthy volunteers, restricted to the parietal, occipital, and temporal lobes (Sandwich Estimator toolbox, height threshold $p = 0.005$ uncorrected, extent threshold $k = 0$ voxels, voxel size = 2 × 2 × 2 mm).

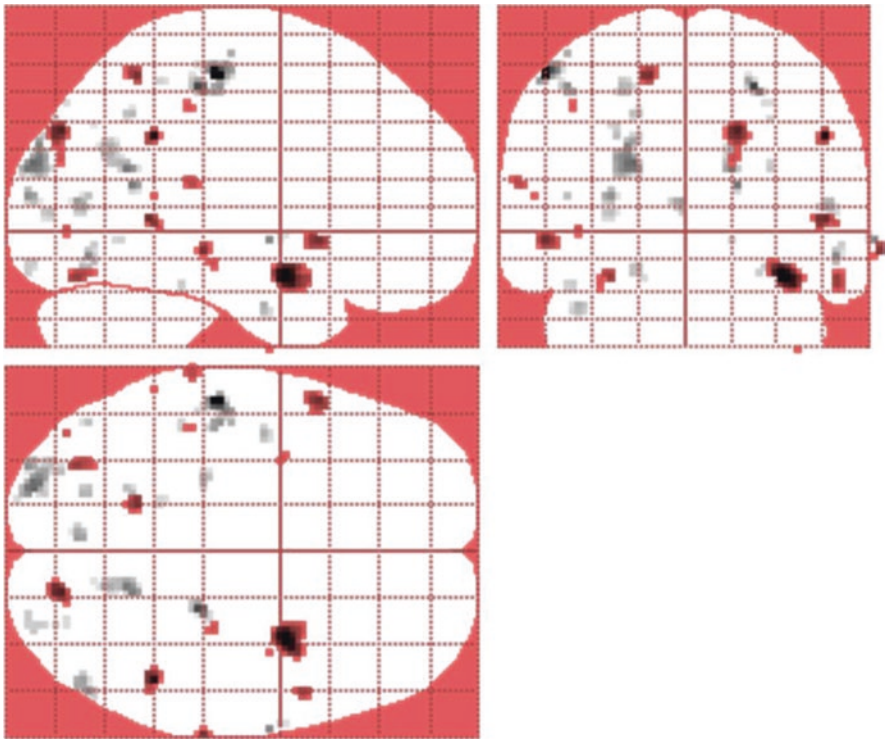

Fig. 3.17 Statistical parametric map projections simultaneously showing increased (black) and decreased (red) regional cerebral blood flow in chronic whiplash-associated disorders patients compared to healthy volunteers, illustration derived from Fig. 3.16a, b by making one of the two images transparent and then superimposing the images on top of each other

Table 3.1 Clusters showing a decrease in the regional cerebral blood flow in chronic whiplash-associated disorder patients compared with healthy volunteers

Cluster		Peak			
Region	*k*	*Z*-value ± SD	*x*	*y*	*z*
R. superior temporal gyrus	86	3.14 ± 0.43	35	−1	−16
R. cuneus	39	2.91 ± 0.28	17	−78	36
L. superior temporal gyrus	25	2.87 ± 0.21	−52	11	−5
L. precuneus	15	2.90 ± 0.23	−15	−50	53
R. middle temporal gyrus	15	2.79 ± 0.18	52	5	−16
R. middle temporal gyrus	13	2.93 ± 0.29	48	−48	5
L. lingual gyrus	12	2.90 ± 0.17	−29	−74	−12
R. supramarginal gyrus	10	2.99 ± 0.38	48	−45	33

Height threshold $p = 0.005$ uncorrected, extent threshold $k = 10$, voxel size = 2 × 2 × 2 mm
Anatomical location and coordinates according to Talairach Daemon database atlas
k number of voxels in the functional area, *SD* standard deviation (copyright 2016 by Vállez García D, Doorduin J, Willemsen ATM, Dierckx RAJO, Otte A. DOI: https://doi.org/10.1016/j.ebiom.2016.07.008. Published by Elsevier B.V. under the open-access license CC BY NC ND [http://creativecommons.org/licenses/by-nc-nd/4.0])

Table 3.2 Clusters showing an increase in the regional cerebral blood flow in chronic whiplash-associated disorder patients compared with healthy volunteers

Cluster		Peak			
Region	*k*	*Z*-value ± SD	*x*	*y*	*z*
L. cuneus	60	2.89 ± 0.21	−21	−88	26
L. postcentral gyrus	43	2.92 ± 0.32	−52	−21	51
R. precuneus	42	2.74 ± 0.14	15	−55	22
R. postcentral gyrus	15	2.85 ± 0.30	23	−29	48
R. middle temporal gyrus	15	2.74 ± 0.15	48	−71	10
L. cuneus	12	2.78 ± 0.13	−3	−73	12
L. middle occipital gyrus	11	2.78 ± 0.15	−29	−91	15
L. precentral gyrus	10	2.73 ± 0.11	−25	−27	46
L. fusiform gyrus	10	2.68 ± 0.10	−41	−9	−21

Height threshold $p = 0.005$ uncorrected, extent threshold $k = 10$, voxel size = 2 × 2 × 2 mm
Anatomical location and coordinates according to Talairach Daemon database atlas
k number of voxels in the functional area, *SD* standard deviation, *R* right, *L* left (copyright 2016 by Vállez García D, Doorduin J, Willemsen ATM, Dierckx RAJO, Otte A. DOI: https://doi.org/10.1016/j.ebiom.2016.07.008. Published by Elsevier B.V. under the open-access license CC BY NC ND [http://creativecommons.org/licenses/by-nc-nd/4.0])

the pain threshold was positively correlated with the right superior temporal gyrus and right parahippocampal gyrus and negatively correlated with the right insula.

The described perfusion alterations outside of the posterior parietal occipital region in this study (elevation in the right posterior cingulate and right precuneus, decrease in the right superior temporal, right parahippocampal and inferior frontal gyrus, the right thalamus and bilateral insular cortex) are of special interest, as most of these are in regions that are directly involved in pain perception and interoceptive processing (insular cortex, precuneus, and posterior cingulate), and indicate that the symptoms of whiplash patients might be a consequence of a mismatch between ascending information from neck structures to midbrain structures, and the later integration of this information in brain regions involved in pain processing, as described in Sect. 2.1.

Regarding the parietal, occipital, and temporal region, it is most interesting that, apart from the clusters of hypoperfusion, also marginal areas of hyperperfusion are observed in this region, assuming that in whiplash patients the brain is trying to compensate for hypoperfused brain conditions by hyperperfusion in the neighborhood of these affected areas, which can be seen as an effect of brain plasticity (Otte 2001a, b, c), and may have been underestimated in previous research.

Note that only upon restricting the SPM data, the adjacent activation/deactivation areas are visible (Otte 2019). If one were to run this via pattern recognition using AI, this information would probably be lost (see Sect. 2.7).

A new aspect in imaging whiplash injury is an MRI approach: diffusion tensor tractography (DTT) based on diffusion tensor imaging (DTI) data. With this special MRI sequence it is possible to image traumatic axonal injury (TAI), defined as the tearing of axons due to indirect shearing forces during acceleration, deceleration,

and rotation of the brain, although conventional brain CT or MRI results are negative.

In a critical systematic review from Jang and Kwon (2018), six cases of whiplash injury (Kwon and Jang 2014; Seo and Jang 2015; Jang and Kwon 2015, 2017; Jang et al. 2016; Jang and Lee 2017) are presented. In all cases, TAI of the neural tracts was diagnosed, but no confounding pattern of vulnerable neural tracts in whiplash injury could be derived from this small and heterogeneous sample size.

3.3 3D Visualization of Regions of Cerebral Activation and Deactivation

The brain regions described by the many functional neuroimaging studies on whiplash syndrome vary to a huge amount, indicating activation and deactivation of brain regions even in adjacent areas. This makes the understanding of the mechanism even more complicated. In a work by Biendara and Otte 2017, the results of these studies were summarized using MRIcroGL 3D visualization software and reassembled in an image showing regions of cerebral activation (hyperperfusion or hypermetabolism) and deactivation (hypoperfusion or hypometabolism) (Fig. 3.18).

The obtained image, as we think, speaks a thousand words: Across the studies there seems to be a consensus on deactivation of the posterior parietal occipital region, whereas a large heterogeneity exists in the other brain regions. Perhaps one reason for this is the changing focus of the studies over history (early studies only looked at hypoperfusion/hypometabolism, see above), another point could be the improved hardware and software of modern imaging devices enabling a higher resolution and a less biased statistical power.

3.4 Excursus on Functional Brain Regions

Which functions the individual parts of the brain take over is certainly dealt with in detail in special books, but at this point a few basic information about the most important regions should be recapitulated (see also Fig. 3.19):

The *frontal region*: Disturbances in the frontal lobe are manifested in fine-motor activity, in marked personality changes characterized by emotional instability and unpredictability (e.g., the so-called joke addiction), lack of drive, or a lack of flexibility in thinking and planning.

The *parietal region*: Lesions in the parietal lobe are manifested by a lack of comprehension, difficulties in reading and writing, problems with the ability to perform calculations, right-to-left confusion or the so-called neglect syndrome, in which patients, for example, do not attract or neglect the right side of the body or do not recognize their arms as their own, respectively. In addition, problems in the ability to understand a spoken or facial expression may result. Also, there are patients with

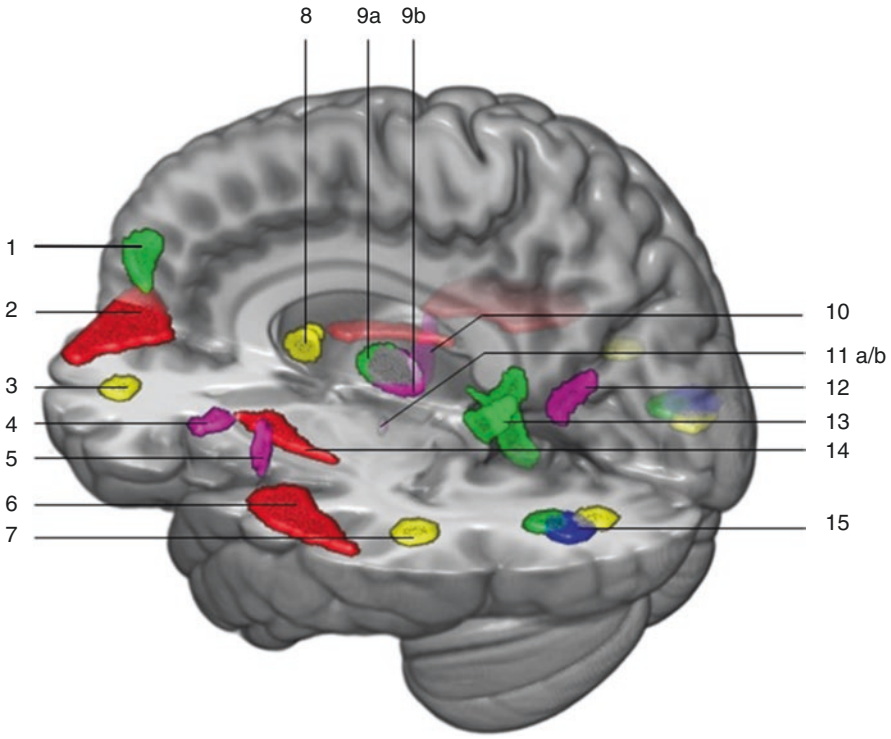

Fig. 3.18 Summary of functional imaging study results over the past 20 years comprising activation and deactivation in whiplash patients. MRIcroGL 3D visualization from Biendara and Otte (2017). The numbers indicate different conditions of cerebral activation in various regions: 1—increased tracer uptake in the right medial prefrontal cortex; 2—decreased tracer uptake in the frontopolar region; 3—decreased tracer uptake in the frontal lobe; 4—decreased tracer uptake in the left frontal inferior gyrus; 5—decreased tracer uptake in the insula at both sides; 6—decreased tracer uptake in the anterior temporolateral cortex at both sides; 7—decreased tracer uptake in the temporal lobe at both sides; 8—asymmetric perfusion in the basal ganglia; 9a—increased tracer uptake in the right thalamus (Linnman et al. 2009); 9b—decreased tracer uptake in the right dorsomedial thalamus (Vállez García et al. 2016); 10—decreased tracer uptake in the right superior temporal gyrus; 11a—increased tracer uptake in the gyrus parahippocampalis posterior at both sides (Linnman et al. 2009); 11b—increased tracer uptake in the right gyrus parahippocampalis (Vállez García et al. 2016); 12—increased tracer uptake in the right superior gyrus cinguli and the right precuneus; 13—increased tracer uptake in the posterior gyrus cinguli at both sides; 14—decreased tracer uptake in the putamen at both sides; 15—decreased tracer uptake in the posterior parietal occipital (also: parieto-occipital) region at both sides. Visualized study results are from Otte et al. (1995a, b, 1996a, b, 1997a, b, c; d, e, 1998a, b, c, d) (shown in blue color), Bicik et al. (1998) (shown in red), Lorberboym et al. (2002) (shown in yellow), Linnman et al. (2009) (shown in green), and Vállez García et al. (2016) (shown in violet). (Biendara and Otte (2017))

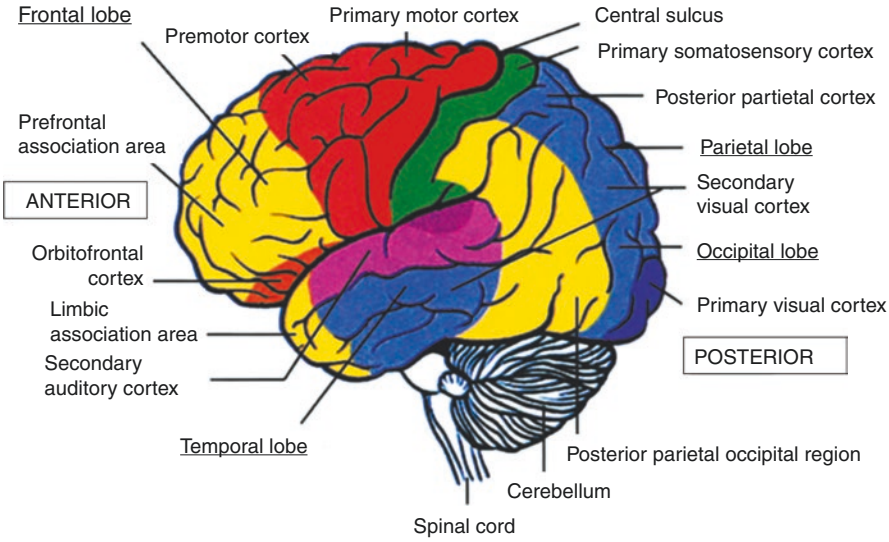

Fig. 3.19 Location of the different brain regions, side view of the brain. (Adapted from Otte (2001d))

lesions in a particular area of the parietal lobe, who, despite their ability to normally recognize visually presented objects, cannot reach for these objects seen, a phenomenon called "optical ataxia."

The *temporal region*: Disturbances in the temporal lobe are expressed in deficits in the conscious perception and interpretation of noise, tones, and sounds. Some patients may, for example, hear a telephone "ring" but not name the meaning of the sound; other patients can, by contrast, recognize nonverbal sounds, but are unable to understand what they are talking about. The temporal lobe also includes the speech or speech recognition, the memory, and the "what" component of the visual system; this is responsible for the identification of objects in contrast to the "where" component in the upper part of the parietal lobe.

The *occipital region*: Lesions in the occipital lobes of the brain show problems in the conscious processing of visual stimuli; typically one also finds visual field defects to cortical blindness. In the part of the occipital lobe which is close to the temporal lobe, there is the function of being able to perceive movements.

The *posterior parietal occipital region*: Lesions in the posterior parietal occipital region manifest themselves in a mixture of the disorders we find in the parietal and occipital regions; often the adjacent temporal lobe is also affected. Thus, the effect of posterior parietal occipital hypoperfusion is impaired spatial ability and blurred vision; it may also cause difficulty in forming thoughts and difficulties not in attending but in disengaging attention once the subject has focused on an object of attention.

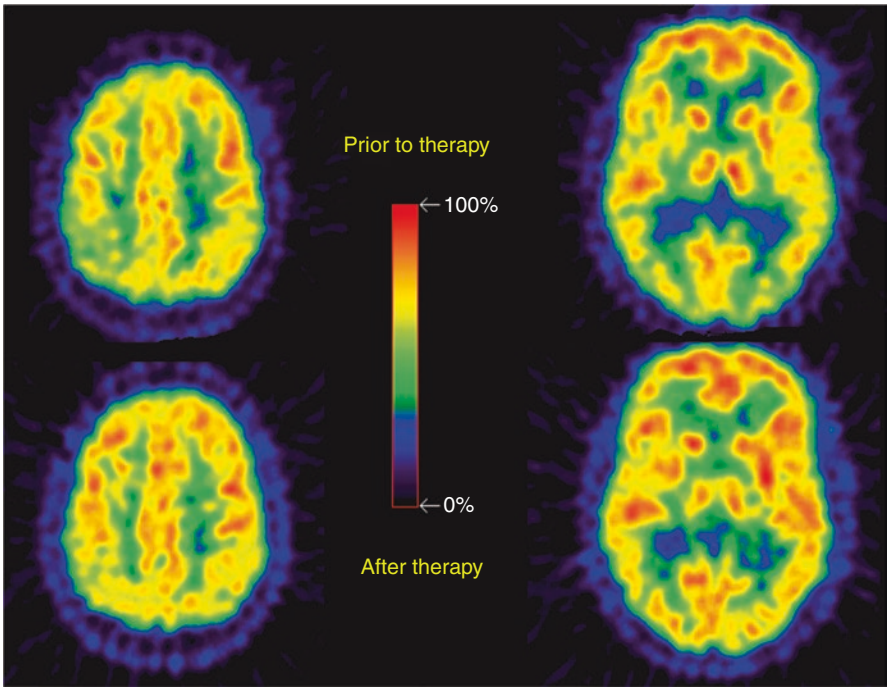

Fig. 3.20 Systemic lupus erythematosus. FDG-PET prior to (*upper row*) and after immunosuppressive therapy (*lower row*). Prior to the treatment, hypometabolism in the right parietal region and both posterior parietal occipital regions can be seen. After therapy, all regions have normal metabolism. Right image side = left brain side and vice versa. (This figure has been published in Otte et al. (1998d), by SAGE Publications Ltd., all rights reserved, ©SAGE)

3.5 Differential Diagnostic List

Lesions in the posterior parietal occipital region can also be found in other diseases, such as the systemic lupus erythematosus (Fig. 3.20; Otte et al. 1997e, 1998d; Weiner et al. 2000; Weiner and Otte 2004), multi-infarct dementia, vascular encephalopathy, sleep apnea syndrome (Miller et al. 1990), cerebral hypoxia (Miller et al. 1990), migraine with aura (Friberg 1991), or Alzheimer's disease (Waldemar et al. 1994). Due to this long differential diagnostic list, the findings in the late whiplash syndrome are disputed. By a purposeful clinical, serological, and/or neurological assessment, the aforementioned other diseases can easily be teased out, however.

It is sometimes stated that whiplash patients—having similar symptoms, especially in cognitive functions, as fibromyalgia patients—have their symptoms based on an underlying fibromyalgia which was already present prior to the whiplash injury. However, a study by Otte et al. (1998c) in this patient group revealed by SPM and SPET a statistically significant hypoperfusion in the frontal lobe at both sides, in the right temporal lobe, and in the head of the right caudate nucleus (Fig. 3.21).

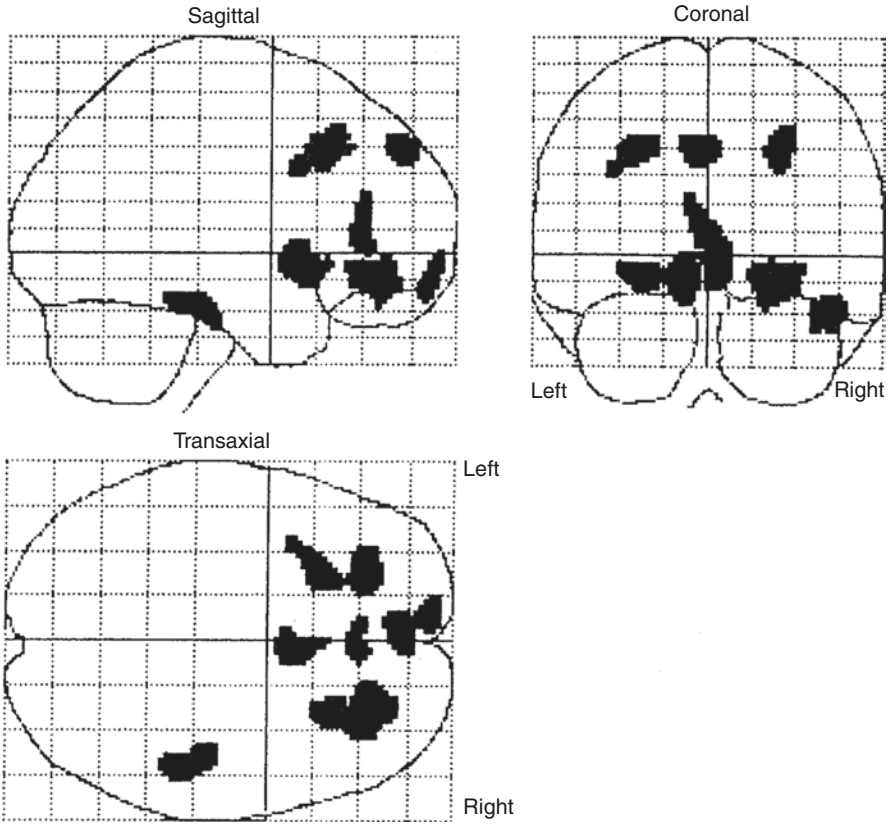

Fig. 3.21 Statistical parametric map projections showing significantly decreased brain perfusion (p-level < 0.01) in 18 patients with fibromyalgia syndrome versus 15 healthy volunteers. Differences are displayed on sagittal, coronal, and transaxial projections: ^{99m}Tc-ECD-SPET. (This figure was published in Otte et al. (1998c), copyright Elsevier (1998). With kind reproduction permission from Elsevier Ltd.)

The results of this study are in keeping with other studies (e.g., Johansson et al. 1995; Costa et al. 1995; Costa and Greco 2004). Lesions in the posterior parietal occipital region were not found in fibromyalgia.

Also, the primary depression is stated as a cause for the late whiplash syndrome (e.g., Alexander 1998). SPET and PET alterations in the primary depression are, however, located primarily in the frontal lobe and not in the posterior parietal occipital region (e.g., Liotti and Mayberg 2001).

3.6 Whiplash Trauma and the Risk of Alzheimer's Disease

Interestingly, the cerebral hypometabolism in the posterior parietal occipital region, which we can observe in late whiplash syndrome, can also be found in Alzheimer's disease (Fig. 3.22).

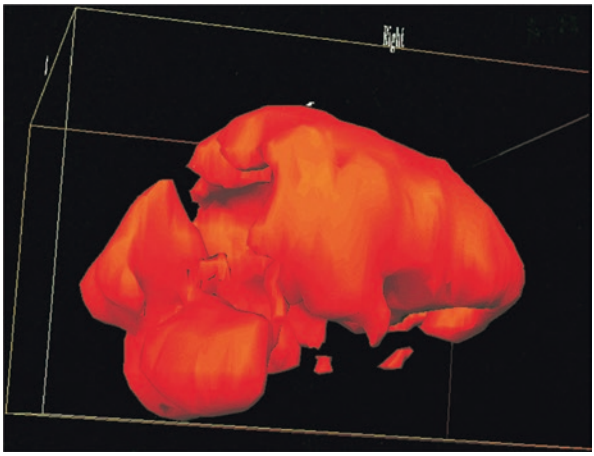

Fig. 3.22 Bilateral parietal/temporal hypoperfusion in Alzheimer's disease and perfusion SPET scan shown as 3D grid. (Adapted from Otte (2001d))

In the literature, there is some evidence of a link between head injury and the subsequent onset of Alzheimer's disease (Otte 1998).

Already in 1928, Martland reported a clinical pattern of cognitive, behavioral, and mood issues in a series of boxers, coining the term "punch drunk," which he describes as follows (Martland 1928):

> For some time fight fans and promoters have recognized a peculiar condition occurring among prize fighters which, in ring parlance, they speak of as "punch drunk." Fighters in whom the early symptoms are well recognized are said by the fans to be "cuckoo," "goofy," "cutting paper dolls," or "slug nutty." The early symptoms of punch drunk usually appear in the extremities. There may be only an occasional and very slight flopping of one foot or leg in walking, noticeable only at intervals; or a slight unsteadiness of gait or uncertainty in equilibrium. These may not seriously interfere with fighting. In fact, many who have only these early symptoms fight extremely well, and the slight staggering may be noticed only as they walk to their corners. In some cases periods of slight mental confusion may occur as well as distinct slowing of muscular action. The early symptoms of punch drunk are well known to fight fans, and the gallery gods often shout "Cuckoo" at a fighter. I know of one fight that was stopped by the referee because he thought one of the fighters intoxicated. Many cases remain mild in nature and do not progress beyond this point. In others a very distinct dragging of the leg may develop, and with this there is a general slowing down in muscular movements, a peculiar mental attitude characterized by hesitancy in speech, tremors of the hands, and nodding movements of the head, necessitating withdrawal from the ring. Later on, in severe cases, there may develop a peculiar tilting of the head, a marked dragging of one or both legs, a staggering, propulsive gait with the facial characteristics of the Parkinsonian syndrome, or a backward swaying of the body, tremors, vertigo and deafness. Finally, marked mental deterioration may set in necessitating commitment to an asylum.

Deposits of amyloid β-proteins can not only be found in cases of dementia pugillistica (the boxers' disease), but also are reported in some cases of patients dying after a single episode of severe head injury (Graham et al. 1996). Tang et al. (1996) found a tenfold increase in the risk of Alzheimer's disease associated with

apolipoprotein E ε4 in combination with a history of traumatic head injury, compared to a twofold increase in risk with apolipoprotein E ε4 alone, whereas head injury in the absence of an apolipoprotein E ε4 allele did not increase the risk.

As shown, due to head restraints of today's cars, whiplash injury can also produce a head impact which may lead to direct brain damage and even pure whiplash trauma in rhesus monkeys without head restraints could be shown to generate direct brain injury due to acceleration and deceleration forces (Ommaya et al. 1968). If severe head injury may trigger Alzheimer-disease-like pathology, an association or interaction with known genetic risk factors for Alzheimer's disease could be speculated in whiplash trauma (Otte 2004). However, this speculation needs to be confirmed by long-term multi-center studies and to date is not very likely. Certainly, a severe head injury is also not comparable with a whiplash injury.

Some authors do not support the hypothesis on exerting dementia of the Alzheimer's type by whiplash injury, e.g., Mehta et al. (1999) and Harwood et al. (1999). Mehta et al. (1999) performed a larger prospective study of a Rotterdam-based cohort of 6645 patients finding no increased risk of dementia for patients with a history of head trauma. In addition, the apolipoprotein E ε4 allele did not modify this relationship.

The fascinating new world of DNA sequencing, which is available for the routine application setting since only few years, may provide further data on this interesting research field, which has also indeed become increasingly relevant today given the demographic development and the incidence of dementias.

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Conclusion

4

4.1 The Dilemma

Already in 1955, Severy and his colleagues (see Sect. 1.4) stated (Severy et al. 1955):

> The low-speed rear-end collision is one of the more common types of urban automobile accidents and it is probably the most misleading. Unlike most types of collisions, the rear-end collision frequently results in minor car damage with major bodily injury. Also, unlike most injury-producing accidents there is generally no visible sign of injury for the rear-end collision victim. Frequently, he is not immediately aware that he has suffered an injury which may require weeks or months for recovery.

In 1994, Carette wrote an editorial on whiplash injury and chronic neck pain in the prestigious *New England Journal of Medicine* (Carette 1994). This editorial was written shortly before the start of functional neuroimaging studies using SPET and PET. Carette concludes:

> … I suggest that we end the futile debate, which has continued for 20 years, over what causes the late whiplash syndrome. The reality is that some patients with a whiplash injury do not recover completely, whether the poor outcome is the result of the severity of the injury, psychosocial factors, or a combination of these causes. Our role is to help our patients adopt an active and positive attitude at all stages after an injury.

Yet today, some 20 years later, whiplash is still an unresolved conundrum.

What triggers such a broad variety of symptoms in an injury caused by only a low velocity accident? Diagnostics of the late whiplash syndrome is a medically and legally challenging endeavor. So far, functional neuroimaging was neglected in contrast to morphological imaging tools, the latter being inconspicuous in most cases, the first showing significant deficits in the posterior parietal occipital region, and decreases and increases in other brain regions, involved in pain processing or trying to compensate for the deactivation in adjacent brain areas. These studies are heterogenous and they only show indirect effects of the reaction to the trauma and its

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posttraumatic developments (Otte et al. 2014). Despite these findings in functional neuroimaging, the late whiplash syndrome remains a medical, political, ethical, and critical issue of actual concern.

Many whiplash patients had to give up their social lives, partnerships, and jobs. Not always are insurance claims the number one issue of their complaints. Frequently, their problems are subject to litigation or pushed—only little better—onto the psychological level.

It should be the primary aim of researchers and clinicians to find ways out of this dilemma.

4.2 Future Research

Future preclinical research utilizing high-standard functional imaging devices and quality image analysis instruments may help to prove the causality of cerebral lesions in whiplash injury. In addition, new functional imaging modalities like functional MRI, magnetic resonance spectroscopy, MR/PET, fNIRS, or SQUID MEG should be introduced to preclinical and clinical research in the field. Most importantly, the clinical studies should be based not only on single cases but also on noticeably larger sample sizes in patients.

Up to now there are mainly four hypotheses for the mechanism of origin for the late whiplash syndrome (Otte et al. 2014):

1. The "whiplash is not existent" hypothesis.
2. The nociceptive-vascular hypothesis. According to Moskowitz and Buzzi (1991) there exists a widespread effect on local vasoactive peptides and the cranial vascular system by stimulation of pain-sensitive afferents in the trigeminal system.
3. The midbrain hypothesis. According to Vállez García et al. (2014) there exists a mismatch between aberrant information from the neck muscles and from the vestibular and visual systems, which information is integrated in the mesencephalic periaqueductal gray and adjacent regions.
4. The traumatic axonal injury hypothesis (Jang and Kwon 2018).

With this book we hope to have shown that the first hypothesis, the "whiplash is not existent" hypothesis, is unrealistic. Quite the contrary, we think that the origin of the late whiplash syndrome is much more complex than any of the aforementioned hypotheses, maybe a combination of all of them, as the brain and its physiological and pathophysiological mechanisms following a whiplash injury are still not well understood.

As far as we do not understand what causes the symptoms, the discussion about this condition and its potential therapeutic approaches (e.g., different physiotherapeutic regimens, as proposed by Michaleff et al. 2014, or Peterson et al. 2018) are needless.

Based on the nociceptive-vascular hypothesis from Moskowitz and Buzzi (1991), we, for instance, propose real-time fNIRS during cognitive tasks and EMG-controlled upper muscle endurance tests, see Sect. 2.1 (Otte et al. 2013), as a possible alternative to PET or SPET imaging: If the hypothesis of nociceptive afferents of the upper cervical spine causing an increased production of vasopeptides especially in the posterior watershed region of the brain applies to whiplash patients, a hypoperfusion could be measured in the posterior parietal occipital region, which may be increased following muscle fatigue or cognitive stress induced by psychological tests, such as the Mini-Mental State Examination, MMSE, or the Wechsler Memory Scale, WMS IV, since the perfusion reserve in this pathological brain region is supposed to be decreased. The effects of physical and mental stress on the cerebral perfusion can be measured in real-time by fNIRS (Fig. 4.1).

Given the encouraging development of high-resolution MRI scanners to new limits (Nowogrodzki 2018), a 10.5T machine has been launched for patients in Minnesota, USA. Germany and other countries want to build 14T human scanners in the near future, and a 21.1T scanner has been developed in the US National High Magnetic Field Laboratory for use in small animals already—we assume that the axonal damage in the brain's white matter, which cannot be imaged by SPET or PET, can be imaged much better by high-performance MRI scanners in the near future. For this approach, mechanistic research with simulation of acceleration/deceleration and shearing processes in brain tissue or brain-tissue-similar substances may be valuable.

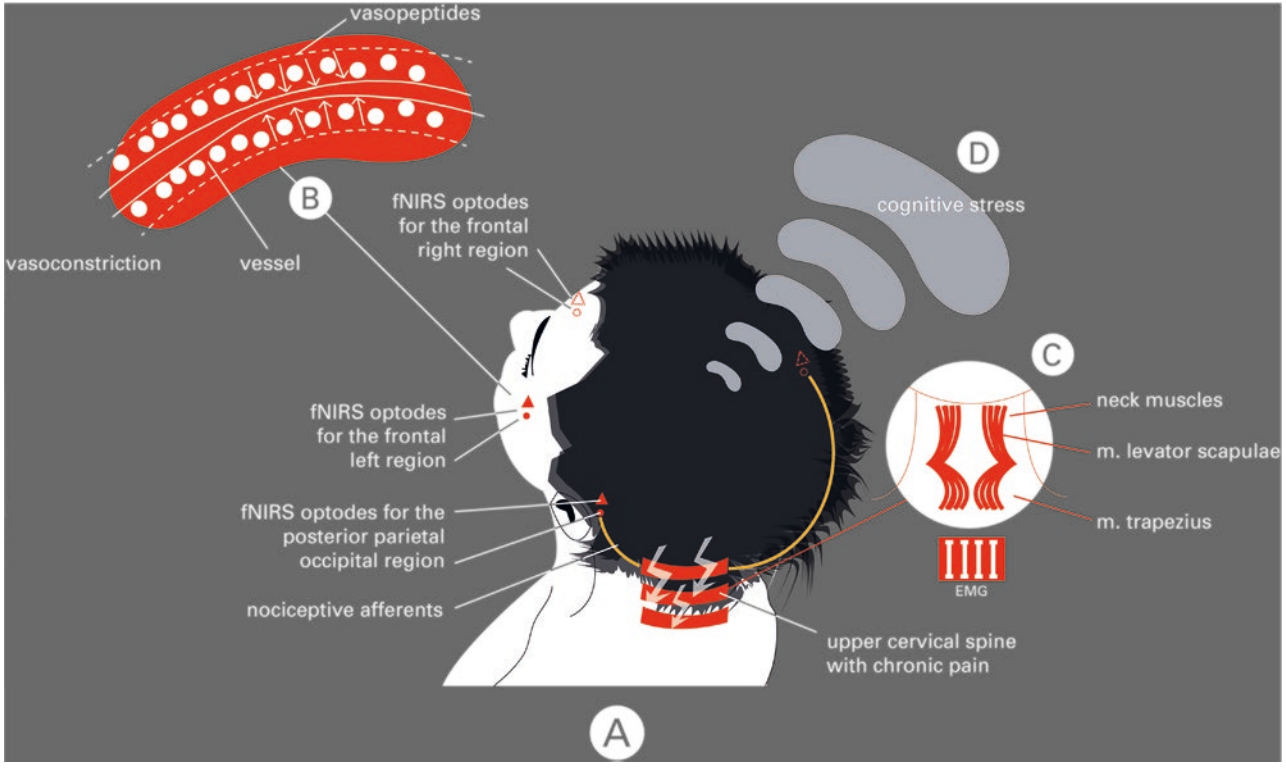

Fig. 4.1 Scheme of one of our newer concepts for the diagnosis of brain perfusion alterations in late whiplash syndrome patients using real-time fNIRS measuring hemoglobin changes during cognitive tasks and EMG-controlled upper neck muscle endurance tests. (**a**) Overview, (**b**) Moskowitz hypothesis, (**c**) EMG-controlled upper neck muscle test, (**d**) cognitive stress induced by psychological tests. (Copyright Otte et al. Adapted from Otte et al. (2013). Frontiers in Optics 2013/Laser Science XXIX, Optical Society of America 2013)

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Clinical Aspects

5

Patients with persistent complaints after a so-called whiplash injury are often left alone. Their complaints are not limited to the musculoskeletal component of the traumatic mechanism, but can also include complaints emanating from the brain, since the brain is inevitably involved in the complex mechanical and pathophysiological mechanism of whiplash injury. The brain symptoms include a spectrum of various different pictures: vertigo, dizziness, concentration, attention and memory deficits, and visual disturbances such as blurred vision or oscillopsia.

Hence, any physician involved, either directly or indirectly, in cases of whiplash patients should be aware of the preponderantly cerebral component of the late whiplash syndrome, leading to a puzzling diagnostic situation at the edge of a controversial medicolegal discussion. One highly recommended way out of this situation is the thorough knowledge of recent research data on functional neuroimaging and its role in this indication.

With the development of high-performance computer systems, functional neuroimaging has gained a firm place at the interface of various disciplines. It is capable of imaging different functions—such as blood flow or glucose metabolism—at different regions of the human brain, thus covering a wide range of different diseases to be investigated. In the past, measuring systems with relatively low resolution were used, but today the two imaging methods SPET and PET in particular offer a high resolution imaging option. These measurement methods are based on the administration of radioactive substances via an arm vein, which then find their way into the brain, where they indicate blood flow or glucose metabolism, depending on the substance administered.

It is possible that the brain shows clear functional changes as seen in SPET or PET, but no abnormalities can be seen in conventional radiological procedures such as CT or MRI, which are only able to show structural (morphological, i.e., anatomical) changes. However, especially in the case of the late whiplash syndrome with cerebral symptoms SPET or PET can reveal already subtle functional alterations. Therefore, SPET or PET are currently the only methods to detect these changes.

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fMRI is under its way to add valuable information to this, but, although it has advantages over SPET and PET in terms of missing radiation, its loud scanning environment and the need for cognitive tests during the scanning process are factors to be considered when the decision on which method is needed has to be made.

The evaluation of studies by functional neuroimaging techniques has undergone significant change over time. SPET and PET studies used to be performed based only on the visual impression of the images. However, this visual assessment alone carries the risk that the evaluation result depends solely on the skill and experience of the assessing physician. Therefore, attempts were made to refine the "reading" of the images in such a way that at least two observers were allowed to make a diagnosis independently of each other, and only in the case of agreement was the assessment considered positive. Often a neurologist was also consulted among the "image assessors." Nevertheless, some early research findings based on visual analysis alone have proven untenable, such as the repeatedly described hypofrontality in schizophrenia (Gur and Gur 1995):

> Several factors may have contributed to the prominence of the hypofrontality hypothesis despite meagre support. Understanding these could help promote progress. The hypothesis is conceptually attractive and sensibly based on clinical and animal studies. The frontal lobes in human beings are highly evolved and regulate complex behaviours, some of which are dysfunctional in schizophrenia. Consequently, the apparently supportive findings with functional neuroimaging buttressed a reasonable expectation in the psychiatric community. The neuroimaging community at the time was impressed by the "hyperfrontal pattern" in normal subjects, and was primed to embrace hypofrontality as indicating a severe mental disorder. The initially limited access by psychiatric investigators to neuroimaging and the expense of such studies have delayed accumulation of large datasets with careful attention to clinical and technical issues. … Finally, the whole hypofrontality and schizophrenia issue should serve as a reminder that psychiatric research, as with the rest of science, must continue to challenge even the most cherished shiboleths.

Nowadays, PET and SPET examinations are not only evaluated on the basis of the physician's visual impression of the images, but also quantitatively. Here, it is possible to draw so-called ROIs in different brain images. This provides information about the uptake of the injected radioactive substance and thus of the blood flow or glucose metabolism for this drawn region. New brain quantification programs—such as SPM—can normalize the brain into a standardized size so that different brains can be compared in a uniform coordinate system. This comparison works voxel by voxel fully automatically, and there is no need to lay out regions of interest any more, which had to be done manually in the pre-SPM era.

Both the (older) ROI technique and the (state-of-art) SPM require data from a reliable normative collective in order to statistically compare and evaluate the image data of a patient or a group of patients—depending on what is to be investigated.

In patients with late whiplash syndrome, early SPET and PET studies showed a statistically significant metabolic reduction in the posterior parietal occipital region of the brain. In individual cases, the patients exhibited also regions with decreased metabolism which were not in the posterior parietal occipital localization, but in

these, no statistically significant group differences to a healthy control group could be determined. Posterior parietal occipital findings can also be seen in other diseases with brain affection, e.g., in systemic lupus erythematosus, in Alzheimer's disease, or in migraine. These other diseases can easily be excluded by a purposeful clinical and neurological assessment. There are also diseases that show a similar clinical component as the late whiplash syndrome, e.g., primary depression. In these diseases, the posterior parietal occipital region is, however, not affected.

In severe traumatic brain injury cases, where patients may initially be in a coma, a relationship to the risk of developing the widely reported Alzheimer's disease has been found. The risk of the accident victim is increased tenfold if certain genetic conditions, namely carrying a specific Alzheimer's gene, are present, while there is only a twofold increased risk in gene carriers who have not suffered a traumatic brain injury.

Functional imaging findings show similar perfusion changes in the posterior parietal occipital region of the brain in patients with late whiplash syndrome as in the onset of Alzheimer's disease. Likewise, direct or indirect brain damage cannot be ruled out in cervical whiplash. Therefore, it can be considered whether whiplash also increases the risk of developing Alzheimer's disease if one has genetic risk factors for it. However, this consideration is so far only an unproven speculation and requires scientific verification.

Interestingly, the early SPET and PET studies have only focused on hypoperfusion/hypometabolism in whiplash patients, since the main clinical symptoms were neurological **deficits** (in attention, memory, and vision). Newer studies, however, also focused on hyperperfusion/hypermetabolism and have exhibited additional brain regions with a disturbed activation pattern, which is directly involved in pain perception and interoceptive processing. They have also revealed that deactivated areas are surrounded by areas that upregulate its activation, presumably to counteract/balance the disturbed perfusion situation of the brain.

With today's PET, SPET, and fMRI scanners and, as mentioned above, with the aid of their convincing image analysis software we have powerful and impressively advancing imaging modalities at hand, helping to better understand the causes and mechanisms of whiplash injury and the still challenging and unresolved question how to best treat this patient population. One approach, following the nociceptive-vascular hypothesis (Moskowitz and Buzzi 1991), may be to eliminate the pain component of nociceptive afferents from the upper cervical spine, which—triggered by vasopeptides—may cause vasoconstriction in the posterior watershed zone, i.e., the posterior parietal occipital region. Another approach may be to eliminate persistent peripheral tissue inflammation in the regions around the spinous process of the second cervical vertebra, as seen in the ^{11}C-D-deprenyl PET studies from the group of Clas Linnman (see Sect. 3.2.3) (Linnman et al. 2011; Aarnio et al. 2021).Thus, pain, pain perception, and interoceptive processing may be the key to this complex disease of its own (Vállez García et al. 2016). In the press release, Dr. David Vállez García, lead author of the study, summarizes the key points very fitting (Press Release from Elsevier (2016)):

> Patients often report these symptoms for years, but if they do see a doctor nothing shows up on the tests. […] Many people start thinking they may be making the symptoms up or trying to make a claim for compensation. It's a tricky situation in which the patient is in pain, the doctors can't explain it and people think they're making it up. We wanted to uncover a real cause of the symptoms – one that could help doctors diagnose and treat it.
>
> With the recent accumulated scientific evidence, we can now say there is something happening in the brain. […] I think our study will improve awareness about the disease, of the public and of medical doctors, and help people with chronic whiplash-associated disorders get the decent treatment they need.

This is our take-home message for any physician in the field, from the radiologist/nuclear medicine physician over the psychiatrist to the general practitioner. Also, different research groups, including experimental animal researchers and biomedical engineers, are highly encouraged to enrich this knowledge.

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