Primitive reflexes in healthy adults and neurological patients : a methodological and clinical study

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A methodological and clinical study

PRIMITIVE REFLEXES IN HEALTHY ADULTS AND NEUROLOGICAL PATIENTS

A METHODOLOGICAL AND CLINICAL STUDY

PROEFSCHRIFT

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door

FREDERIK WILLEM VREELING

PROMOTORES:

Prof. dr. J. Jolles
Prof. dr. J. Troost

BEOORDELINGSCOMMISSIE:

Prof. dr. H. M. van Praag
Dr. R. A. C. Roos (Rijksuniversiteit Leiden)
Prof. dr. A. Staal (Erasmus Universiteit Rotterdam)
Prof. dr. F. Spaans
Prof. dr. J. T. Wilmink

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aan mijn ouders
voor mijn dochters

In science, as in life, Truth is a moving target. To aim as accurately as one can is a personal responsibility.

W. M. Landau

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1 Primitive reflexes in adults: General introduction

1.1 Introduction

In the physiological process of aging a decrease in cerebral functioning is a well known fact of experience and research. Aging is also correlated with an increase in the prevalence of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease and of other neurological disorders, such as vascular dementia and stroke.

Through the years a number of investigations have been done to study the relationship between primitive reflexes (PR) and the normal and pathological aging process of the brain. PR are reflexes that are present in the early stages of human development, they usually disappear with increasing age and may reappear in senescence or with neurological disease.

PR have been supposed to be of (clinical) interest in different ways. Firstly, PR are thought to be pathognomonic signs of certain neurological diseases. Secondly, PR are considered as localizing signs of brain pathology. Finally, it is stated that PR are signs of a reversed ontogenetic development (*retrogenesis*), by loss of cortical control over lower centers. However, for different reasons much is still unclear about the nature and clinical significance of these signs in normal and pathological aging.

In this thesis an attempt is made to bring more clearness into these questions. In the remaining part of this introduction the problems in the study of PR will be further discussed. Questions arising from these issues will be formulated and will result in various experimental studies.

1.2 Primitive reflexes: Definitions

Primitive reflexes (PR) are brainstem-mediated, complex, automated movement patterns which develop during gestation, are present in the newborn and are elicited readily during the first half year of life. With central nervous system maturation PR activity is suppressed during the second six months of life. Such is the definition given by Capute, a child neurologist.[1]

In the realm of developmental or child neurology the clinical importance of the examination of PR is beyond discussion. The appearance and vanishing of these signs are useful clinical parameters for the development of the child. Capute distinguishes three categories or phases based upon the age at which these reflexes appear and are suppressed. PR–I represent those responses that occur during intrauterine life. A startle-like response that appears at the 5th and disappears at the 10-12th week of gestation is an example. Standardization and validation for predictiveness of these signs might well result in the evolution of an intrauterine reflex profile (IURP) which may be helpful in identifying 'high-risk' embryo's. Techniques like sonography may be of great value in studying these signs. PR–II represent those reflexes that are the neurodevelopmental substrates to pediatricians; examples are the Moro and Galant reflexes, the plantar grasp, and the asymmetrical tonic neck reflex. A primitive reflex profile (PRP) of quantified reflexes can be indicative of a delay in neuromotor development.[2,3] PR–III represent the equilibrium and righting reflexes that appear when the PR–II responses are suppressed, for instance the Landau reflex. The importance of quantification, standardization and validation of a PRP in the examination of the developing child is stressed.[4,5]

Touwen[6] judges the term *primitive reflexes* as an inadequate explanation of the activity of the infant's brain, because it expresses that "the infant's brain is considered to be a primitive –underdeveloped, incompetent, deficient– edition of the adult brain". In the first place, however, when the term *primitive reflexes* is used in this thesis, (most of the time) we refer to PR in adulthood. Secondly, the term *primitive* as it is defined in Webster's dictionary certainly does not support such a view. Touwen's native language (Dutch) may have played a role in his judgement: the Dutch word *primitief* not only means 'original', 'primarily', or 'pertaining to an early stage' but it can also mean: 'awkward' 'crippled' or even 'ill-bred'!

Touwen also rejected the word 'reflexes', because it would suggest that "the (infant's) brain is considered to function on a reflex basis –'reflex' being used to contrast with cortically controlled voluntary activity". Although only very few supporters of a purely reflexological concept of the (infant's) brain are left, it cannot be denied that in the infant as in the adult the process of a reflex action, as defined above, certainly for the greater part takes place without consciously being influenced. So, without denying the enormous complexity of the brain and certainly not supporting solely the purely mechanistic 'reflex-paradigm' of brain activity, we shall nevertheless maintain the term *primitive reflexes*.

The synonyms that are used in child neurology are: *embryonic*, *fetal*, and *neonatal* reflexes, terms referring to a certain stage in the development of the child in which these signs are present; the more general name *developmental* reflexes is mentioned quite often. In the neurology of adulthood the following terms are named: *regressive*, *archaic*, or *atavistic* reflexes, *cortical disinhibition signs*, and *(frontal) release phenomena*, in which each appellation may express the author's conviction about the cause or nature of these signs.

In a thesis about primitive reflexes these terms should be thoroughly defined. For this purpose the definitions of Webster's New Collegiate

Dictionary is followed:

> *Primitive* is defined as ".. 1. *adj*. of, pertaining to or characteristic of the earliest period or origin of something || (biol.) of or pertaining to an early stage of development".
>
> *Reflex* is defined as ".. 3. an act, as a movement, performed involuntarily in consequence of a nervous impulse transmitted from a receptor, or sense organ, to a nerve center and outward to an effector, as a muscle or gland; also the whole process (reflex action) culminating in such an act".

When in this thesis the term *primitive reflex* is used, it refers to the whole process of a reflex action that 1. is physiological and generally present in the early stages of ontogenic development, 2. tends to disappear with maturation of the central nervous system and 3. may reappear in senescence and/or with (neurological) disease. Unless otherwise indicated the PR in the text refer to the signs as they were examined in adults.

1.3 Primitive reflexes: what do they tell us?

The clinical value of PR in the neurological examination of adults is far from established. Some authors are convinced that PR are highly sensitive and/or specific signs for certain diseases or for focal processes,[7-10] others consider PR as normal phenomena of senescence.[11] Table 1.1 lists the various conceptions about the clinical significance of PR in adulthood. The judgment if PR are of any clinical significance differs from a definite 'no' as for instance from Landau in his series on 'Clinical neuromythology', to an equally definite 'yes', e.g., from Brakha, who considers (some) PR as sensitive and specific localizing signs.[12,13]

How one considers the value of PR depends partially on the 'glasses' by which one looks at them. It is obvious that a child neurologist will consider PR as milestones in the development of infants. However, when looking at PR in adults, the 'normal development' from young adulthood to senescence is by far not as strictly established as in childhood, and the individual variation may be enormous. The number of variables that have come into each individual life is large, making it impossible to predict with some reliability when exactly what sign of senescence will show up. As to PR this means that if they are considered as signs of normal aging, they will appear at various ages. This brings us to the problem of what exactly is 'normal' aging. Rowe and Kahn have initiated new thoughts about normality, which can be subdivided into 'usual' and 'successful'.[14] It remains to be seen whether in pathologic or accelerated aging PR occur more often. This will be discussed in one of the following chapters.

Table 1.1. Some conceptions about the clinical value of PR in adults

Primitive reflexes
- are signs that are normally present in adulthood
- are present at any age, but increase with senescence
- are signs of an accelerated or abnormal way of aging
- indicate a diffuse cerebral dysfunction
- indicate cortical disinhibition
- indicate cortical atrophy
- indicate cognitive disturbances or dementia
- indicate ADL and behavioral dysfunction in Alzheimer patients
- are parameters for the level of consciousness
- are localizing signs in brain lesions
- are much more prevalent in neurological diseases, such as (extra)-pyramidal tract syndromes, frontal lesions, intoxications, and cerebro-vascular problems
- are often present in some psychiatric disorders, like schizophrenia and autism
- have a prognostic value in predicting the outcome of rehabilitation in stroke patients
- indicate a developmental disturbance of the brain
- indicate reversal to a lower ontogenetic level ('retrogenesis')
- indicate reversal to a lower phylogenetic level

The fact that some PR often appear with increasing age and other PR are hardly ever present in healthy aged, could indicate different natures of the signs, indicating the need for research on a broad specter of PR in well defined populations. The way how PR are scored seems to be of importance too. Some investigators only note the mere presence of the reflex, others consider scoring of the amplitude or persistence (the lack of habituation) of the sign of importance.[15,16] In some papers a high prevalence of PR, in connection with other signs, was found to be indicative of diffuse cerebral dysfunction, cognitive decline or dementia.[7,17,18] However, these PR can also be found in normal aging. Data on PR related with cortical atrophy are controversial.[19-21] PR in psychiatric disease have only sporadically been examined, and their clinical meaning is unclear.[22-26] Many of the other reports on PR concern small numbers, often without controls. Exceptions to this are the reports of Shaw et al. on the development of PR after cardiosurgery.[27-28] The patients were examined before and after the operation, being their own perfectly matched control. However, the origin of the PR which developed post-operatively is unknown.

1.4 Primitive reflexes: where do they come from?

It is hypothesized that PR in adult subjects represent release phenomena, due to a decrease in higher cortical control over lower centers. According to this hypothesis, reflexes that exist in earlier stages of ontogenesis are suppressed as the brain matures, to reappear with diminution of cerebral inhibition: "once a man, twice a child". Delwaide and Dijeux[17] indeed found some evidence in their longitudinal study of Alzheimer patients that primitive reflexes reappear in the reverse order in which they develop in childhood. This reverse onto-genesis or 'retrogenesis' had been predicted by de Ajuriaguerra,[29] following the Jacksonian postulate of 'dissolution' of the brain. In his writings on different levels of dissolution, however, Jackson states: "We rarely, if ever, meet with a dissolution from disease which is the exact reversal of evolution. Probably healthy senescence is the dissolution most nearly the exact reversal of evolution. In local dissolutions of the highest cerebral centers there plainly cannot be the exact antithesis of evolution."[30] There seems, however, to be some tendency for PR to reappear in a certain sequence with the development of a diffuse cerebral disorder like Alzheimer's disease. PR can be divided into the so-called 'nociceptive' reflexes (elicited by a noxious stimulus, e.g., a hammerstroke), and 'prehensile' reflexes (with a prehension response, e.g., grasp or suck).[9] The nociceptive signs (snout, glabella tap, and palmo- and pollico-mental reflexes) appeared in the early stages of the disease, but they were less generally present in the later stages in the study of Franssen et al.[9]; in more severely demented patients an increased prevalence of the prehensile signs (suck, grasp and rooting reflexes) was found. Thus, it is still not clear whether and which PR are pathological signs or merely phenomena of normal aging. It is possible that some (subgroups of) PR must be considered as patholo-gical phenomena, given certain circumstances as age and previous conditions.

1.5 Primitive reflexes: how to examine them?

A major problem when comparing various studies on PR is that the values given for the prevalence and incidence of these signs vary among the research papers. One important reason for this is the lack of standardization in how these reflexes are elicited. The circumstances under which the reflexes are elicited are usually not described and seldom applied in a standardized fashion.

If a description is given, it is often too consise and may it differ from author to author. Moreover, it is not clear what –if any– instructions are given to the subject.[17,18,31] Another problem is that investigators also differ in the interpretation of particular reflexes and their scoring, with research papers showing diversity in the assessment in quantitative terms. For instance, Otomo[32] did not evaluate the palmomental reflex as positive when fewer than five successive contractions were found. Others, using less strict criteria, found a greater prevalence of this reflex in normal subjects.[15,16,33,34] Several authors suggested that the intensity and/or the persistence of the response, i.e., the lack of habituation, might be of more significance than its mere presence.[9,31,34] A third problem is that the PR examined vary from study to study, and it is not often that more than one or two PR are investigated. A 'primitive reflex profile' (PRP) for a broad range of signs has been established in child neurology.[4,5] However, in adult neurology, it is only recently that such a PRP, including a scoring system, has been described.[9,31] Lastly, there is little information about interobserver and intraobserver reliability, even though the need for it is well-recognized.[7,31,35,36]

In sum, for the study of PR it is necessary 1. to design a protocol for the application of PR on adults, in which the instructions to the patient and the doctor, and the way of eliciting and scoring of the reflexes are standardized, in order to obtain a diagnostic tool with a high inter- and intraobserver reliability. 2. to gather normative data on the prevalence of PR in healthy volunteers of different age groups and 3. to assess the prevalence of PR in young, middle–aged and senescent patients with various neurological conditions.

1.6 Aim of the study

In the preceding paragraphs, it has been demonstrated that there is much about PR that is not yet clarified and that the available data show a great variability due to several causes. The aim of this study is to bring more clarity into this field. Especially the following questions need to be answered. Are all PR in this study signs of the normal aging process? Which are and which are not? Are (some) PR the consequence of diffuse or local brain damage? Are (some) PR more or less specific for certain diseases?

In chapter 2 a brief historical overview is given about the clinical studies on the individual PR that are examined in this thesis. An attempt has been made to draw a preliminary conclusion about the clinical value of each individual reflex on the basis of the studies up till now. Only the relevant studies are quoted and some historical remarks are made.

In view of the methodological differences in the literature on how to standardize the examination of PR, a newly designed protocol for a broad battery of primitive reflexes (BPR) is presented in **chapter 3**. The PR that were included in the battery are in the first place those that are frequently described in the literature. A second category consists of PR that are infrequently observed and that are scarcely mentioned in studies of adults. The third category are PR well known in child neurology that are of potential use in studies on adults. Studies on inter- and intraobserver reliability in various groups of patients are carried out. Kappa statistics are used to assess the agreement. A scrupulous description of the elicitation and scoring of both amplitude and persistence of each separate reflex is given, in order to lay down how PR can be examined in a reproducible way.

The BPR was then applied in a cross–sectional study on two hundred and fifty-six healthy subjects, who were assigned to different age groups (**chapter 4**). This study was done in order to gather normative data on the prevalence of PR in normal adults, and to analyze the possible influence of 'biological life events' (BLE) on the prevalence of PR in otherwise healthy people (BLE are health related factors with possible influence on cerebral functioning, e.g., mild closed head trauma, general anaesthesia etc.).[37]

Chapter 5 describes the examination of the prevalence of PR in a group of patients with age-associated memory impairment (AAMI). The findings were compared with the PRP of two groups of control subjects, one with and one without BLE. The aim of this study was to examine the possible influence on the brain, as expressed by PR, of –until now unknown– agents that are related to AAMI, and to compare the findings with the effects of the known agents on PR in BLE subjects.

The application of the BPR on two groups of demented patients, one with Alzheimer's dementia and one with vascular dementia, is described in **chapter 6**. This study was carried out in order to assess the PRP of two groups of patients with dementia from different origin. Two subgroups of PR were distinguished: the nociceptive and the prehensile signs. The aim of this study was to find out 1. what are the differences with age matched controls, in other words: what is the influence of pathological aging versus normal aging on PR? 2. do the PRP in dementias of different origin differ? 3. do nociceptive reflexes prevail over prehensile reflexes in these mildly demented patients?

Chapter 7 examines the prevalence and possible diagnostic and therapeutic implications of PR in patients with Parkinson's disease. The aim of this study was 1. to establish the presence of PR known to be frequently present in this condition (glabellar, including a variant the nasopalpebral, and the snout reflexes) and their clinical value, 2. to evaluate the influence of levodopa therapy on the presence of PR.

In **chapter 8**, the results are reviewed and discussed, and final conclusions are drawn. Some recommendations for future research are done.

In some of the investigations presented here, a number of other reflexes was studied as well. These concerned the so-called 'rare' reflexes, which represent a group of heterogeneous signs that are observed very infrequently. However, some authors consider a few of these reflexes as pathognomonic signs (e.g., the abductor digiti minimi reflex for striatal lesions), localizing signs (e.g., the finger–abduction reflex for deep frontal lesions)[38]. This category of reflexes is not discussed in this thesis, interesting though they are. They do not represent a coherent group of signs like PR, which can all be thought of as evidence for brain dysfunction. Furthermore, they are too seldom observed to present any conclusive data at this stage of the research project that is still going on. Finally, paying due attention to this wide variety of other reflexes would make the thesis about twice as voluminous. The findings concerning 'rare' reflexes will therefore be dealt with in future papers.

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2 Primitive reflexes in adults: An overview

2.1 Introduction

The modern theory of reflex action was founded by René Descartes in the 17th century. He suggested that certain actions resulted from 'reflection of spirits' within the brain, in which the will or soul took no part. Descartes was probably the first to use the term *reflect*. This mechanistic explanation was followed by Thomas Willis, who also used the term *reflection*, and who was the first to presume nervous communication outside the brain, again without the intervention of the soul. Prochaska at the end of the 18th. century postulated a 'sensorium commune' that mediated the reflection of an external stimulus via the sensory nerves into the motor nerves. A hundred years later the publications of Westphal and Erb on the clinical examination of tendon reflexes ushered in a period of 'reflexology' in neurology. The mechanistic postulate had definitely gained victory over the classical vitalism of Galen, that had been supported by Whytt, Hall, and Pflüger (who used the term *Rückenmarkseele)* in the 18th and 19th century. A great amount of all sorts of reflexes were '(re)discovered' or, to speak with Wartenberg: "the open season for hunting the reflex" had begun. Not only numerous new tendon reflexes and variations on Babinski's sign showed up, many primitive reflexes were also described in the period of thirty years around the turning of the 19th to the 20th century.

The term *primitive reflexes* was first used by Buckly[1] in 1927: "The term primitive reflex is used to designate a mechanism by which a particular type of response is brought about by the activity of either a single nervous arc or several nervous arcs, such reflexes as have been observed in embryonic and later life in lower forms of animals and in human beings. (..) Neural excitations of sufficient duration and intensity to dominate the activity of the organism for the moment, and capable of neutralizing or counteracting the effect of an excitation which normally would bring about the response in question, are regarded as inhibitory. (..) In the adult, the chain of events involved in inhibitory processes becomes more complex as experiences multiply through training and habit. It would seem, therefore, that inhibitions in their simplest forms, as in childhood primarily, are largely sensory. Stimuli of smell, taste and touch, which initiate the sucking and swallowing reflexes, are strongly inhibitory against other stimuli, with the probable exception of painful stimuli, as is shown by the soothing effect of feeding upon the restless infant. (..) The higher the position in the phylogenetic scale and the greater the advancement in the development of the individual, the more potent becomes the value of inhibition to the organism. (..) In normal states, primitive reflexes may operate as pure reflexes; they may be initiated as pure reflexes and terminate as instinctive acts or emotional responses (the line of separation between these cannot be sharply drawn); they may become more or less completely under control through direction or choice of action and, therefore, may terminate as volitional acts. (..) Complex acts terminating as adaptive responses without previous training or representation in consciousness are assumed to constitute instinctive acts. From this point of view, therefore, some reflex acts may be regarded as instinctive acts. All instinctive acts are assumed to be constituted of primitive reflexes."

A wide variety of eponymous, primitive signs were described in clinical studies; many of them showed an astonishing resemblance, thus undergoing the same fate as Babinski's sign. Wartenberg[2] however, in his classic work 'The examination of reflexes: a simplification' pointedly instructed that similar reflexes, regardless of site or type of stimulus, must basically be considered the same reflex if the motor response is uniformly performed by the same muscle or muscle group. Some of these reflexes were considered pathognomonic for certain diseases, others were thought to be useful as localizing signs. In another classic paper, 'Development reflexes: The reappearance of fetal and neonatal reflexes in aged patients' by Paulson and Gottlieb[3] the reappearance of these responses was first related with diffuse cerebral dysfunction, rather than with focal processes. In the vision of the authors ".. the general weakening of higher inhibitory and regulatory centers in the brain apparently allows numerous reflexes present in fetal life to reassert themselves".

The fourteen PR that have been examined in the various studies described in the chapters 3-8 will be discussed in an alphabetical order. The reflexes that were studied can be divided into three categories. In the first place, PR were taken that are often mentioned in the field of aging research, such as the *glabellar tap*, *palmar grasp*, *palmomental*, *rooting*, *snout*, and *suck* reflexes. The second category consists of PR which are less frequently described and not usually applied in the routine examination, but which are mentioned by some authors in relation to particular brain abnormalities: the *head retraction*, *nuchocephalic*, and *pollicomental* reflexes. The third category consists of PR which are well known in child neurology and which may be useful in the examination of adults, according to scarce reports. These are the *asymmetrical tonic neck*, *plantar grasp*, *mouth–open finger–spread*, and *palmar* and *plantar support* reflexes. Many other reflexes that have been mentioned in the literature deserved no consideration. Some of them are simply not applicable to adult persons for physical reasons, like the Moro reflex or the stepping reflex; some are not primitive reflexes following the definition in the chapter 1, like the *corneomandibular* reflex: Ansink[4] found the sign present in only one of 65 healthy infants. Various other, rare reflexes have also been examined in some of the studies in this thesis. The history and results concerning these signs will be published elsewhere.

A standardized protocol that describes how to elicit and score each reflex is given in the appendix. The protocol has been used throughout all studies that are described in this thesis.

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2.2 Description of primitive reflexes

In the following sections, some synonyms for each PR and the most commonly used dutch translation, a brief description of its elicitation, the publication in which the reflex was first mentioned, and a few core references are given, followed by an overview of the relevant literature and the conclusions that can be drawn so far for each separate reflex. For the literature referred to in the following sections the reader is referred to the alphabetical bibliography.

2.2.1 Asymmetrical tonic neck reflex (ATNR)

Synonyms	Magnus(-de Kleijn) reflex (Asymmetrische tonische nekreflex).
Elicitation and response	Turning of the head to one side causes an increase in the ipsilateral and a decrease in the contralateral extensor muscle tone.
First description	Magnus and de Kleijn (1912)
Core references	Hirt S, Am J Phys Med (1967) Warren ML, Am J Occup Ther (1984) Aiello I et al., Ital J Neurol Sci (1992)

The first authors examined the ATNR in animals in which they could omit the influence of reflexes of the labyrinth by destroying it. The ATNR was also demonstrated in an infant and in adults whose hemispherical function had been more or less eliminated by disease. Turning the head was supposed to activate the receptors in the neck muscles.

Simons (1923) was the first to apply the ATNR on humans. He found no correlation between cortical damage and the ATNR, but it was clearly present in patients with diseases of the pyramidal system. Walshe (1923) found an increase in the amplitude of the reaction when the subject actively turned the head or when resistance was exerted against the turning, and considered it a pathological reflex, related to spastic hemiplegia. He noticed that the latency period could last from 1–6 seconds. The ATNR is present in infants most clearly from 2 weeks, peaks in activity by two months, to decline smoothly in the first year, according to Capute et al. (1984).

Parmenter (1983) was the first to use a standardized rating scale for the ATNR in children, which was applied by Zemke (1985) in the scoring of developmental rates in preschool children. In normal children there was an increasing inhibition with increasing age. Capute et al. (1984) used the ATNR in a PRP. He hoped that the standardization of this examination technique would complement the traditional infant neurological examination and would allow PR to become a useful adjunct to the prediction of motor disability in early infancy. Morrison (1985) used the primitive reflex profile of Capute in his study on neurological dysfunction in learning disabled children. He found significantly more PR with the exception of the ATNR.

Hirt (1967) demonstrated the ATNR in the normal human adult. Aiello et al. (1992) performed a neurophysiological study on the interaction of tonic labyrinth and neck reflexes in man. In a comparative study on the presence of the ATNR in adult hemiplegia, Warren (1984) concluded that there was no difference in the intensity of the reflex between normal adults and patients with hemiplegia. The ATNR should be viewed as a normal response to nervous system distress rather than a symptom of pathology. This is in contrast with the findings of several other authors in the older literature (Schuster, 1923; Dawidenkow, 1926). In the physiotherapeutic treatment for hemiplegia following the Bobath method the ATNR is used as a diagnostic tool to assess spasticity and in facilitation techniques for the execution of certain movements (Kollen, 1982).

The main conclusion so far is that the ATNR is a useful sign in child neurology and that it may be useful in the treatment of hemiplegic patients. However, its practical value in the clinical examination of the adult neurological patient is not yet established.

2.2.2 Glabellar (tap) reflex (Glab)

Synonyms	Blink, orbicularis oculi, frontal, supra–orbital, ophthalmic, trigeminofacial, trigeminal–orbicular, Guillain reflex, Myerson's sign (Glabella tap reflex).
Elicitation and response	Tapping the forehead causes winking or blinking of the eye(s).
First description	Overend (1896)
Core references	Rushworth, J Neurol Neurosurg Psychiatry (1962) Zametkin et al., Ann Neurol (1979) Fine et al., Neurology (1992)

Much of what is known presently was predicted in Overend's publication. Many authors described similar facial reflexes in the years to follow (McCarthy, 1901; von Bechterew, 1902; Guillain, 1920; Simchowicz, 1922). Wartenberg (1945) proposed to simply use the term *orbicularis oculi reflex..* He believed it was a myotatic reflex, in contrast with the original teleological hypothesis that the reflex is a defense mechanism. The nasopalpebral reflex (*Nasenaugenreflex*), a variation of the Glab, was first described by Simchowicz (1922), together with the *nasomental* reflex (*Nasenkinnreflex*).

The nasopalpebral reflex was considered to be a physiological sign, but the nasomental sign was thought to represent supranuclear pathology.

Kugelberg (1952) was the first to analyze the reflex electrophysiologically. He found an early and a late component in the bilateral reflex response, the first being myotatic/proprioceptive and the second defense/nociceptive, thus confirming both Overend's and Wartenberg's opinions. The work of Rushworth (1962) confirmed this. More studies show that there is general agreement that the R_2 response is a cutaneous polysynaptic reflex. However, whether the early response is myotatic (Kugelberg, 1952) or cutaneous (Shahani, 1970) in nature is still in dispute. There is more controversy about the origin of R_1. Though Kugelberg believed that R_1 is monosynaptic, Shahani(1972),and Penders and Delwaide (1971) mentioned that R_1 is polysynaptic. The reflex was found abnormal in the Wallenberg syndrome in an electrophysiological study by Kimura and Lyon (1972).

The habituation index of the glabellar reflex has been studied in (drug-induced) parkinsonism, dementia, senile chorea and hyperosmolality in diabetes (Pearce, 1974; Caraceni et al., 1976; Ferguson, 1978; Tachibana et al., 1990). In Huntington's chorea it was suggested to serve as a detection method for individuals at risk by Esteban and Giménez–Roldán (1975). Bánk et al. (1992) found alterations in the trigeminal afferents and/or polysynaptic pathway in the brainstem in measuring the blink reflex in migraine patients. In a recent study by Matsumoto et al. (1992) a correlation was found between the habituation index and the scores for both the neurologic disturbance and the impairment of daily activity in patients with Parkinson's disease.

In addition to neurophysiological investigations in the mechanism of the reflex, several studies concern the use of the glabellar reflex as a clinical sign. Guillain et al (1924), Myerson (1944) and Garland (1952) found that in normal subjects the degree of lid closure evoked by repetitive glabellar taps diminishes rapidly and that habituation is absent in patients with Parkinson's disease or parkinsonism. This lack of habituation was also demonstrated in many other clinical studies (Rushworth, 1962; Pearce et al., 1968; Paulson and Gottlieb, 1968; Sanna and Messina, 1967; Penders and Delwaide, 1971). The original observation that cortical infarcts can cause transient loss of the blink reflex was confirmed by Kimura (1974), but Overend's comment that it was difficult to observe in Parkinson patients was sharply contradicted by the findings above and by the results of Esteban and Giménez-Roldán (1975). Tweedy et al. (1982) found the reflex disinhibited in a high percentage of patients with Parkinson's disease and in vascular and Alzheimer's dementia. The persistence of the reflex in parkinsonian patients was found to reverse under the influence of different anti–parkinson drugs (Klawans and Goodwin, 1969; Penders and Delwaide, 1971; Messina et al., 1972; Sandrini et al., 1985).

To date, if uninhibited, the reflex is considered a sign of Parkinson's disease and of other supranuclear pathology, such as Alzheimer's disease and multi-infarct dementia.

2.2.3 Grasp reflex, palmar (GrPa)

Synonyms	Réflexe saississeur or réflexe de prehension, tonic innervation, Zwangsgreifen (Palmaire grijpreflex)
Elicitation and response	Stroking the palm of the hand causes a grasping reaction.
First description	Janischewski (1914)
Core references	Paulson and Gottlieb, Brain (1968) Tweedy et al., Neurology (1982) De Renzi and Barbieri, Brain (1992)

The first author found the reflex in patients with hemiplegia and parkinsonism. He located it just above the frontal subcortical nuclei in the contralateral hemisphere; the appearence was considered the consequence of a lesser activity of the overlying cortex. Because according to Seyffarth and Denny-Brown (1948) the infantile grasp reflex is not identical to the response seen in adults with contralateral frontal damage, they suggest to use the name *forced grasping* (reflex). Others understood by the terms *forced grasp(ing)* and *groping* the grasping reaction elicited by visual input of a moving or stationary target to the patient with focal frontal or diffuse bilateral cerebral lesions (Mori and Yamadori, 1985).

From experimental investigations it was concluded that the grasp reflex was dependent on a lesion of area 6 (Pollack, 1960). Though it now appears well established that the responsible cortical region is the supplementary motor area, Pfeiffer (1964) studied brains after autopsy and found the grasp reflex not only caused by contralateral frontal damage, but also in cases of ipsilateral lesions in the basal ganglia. It was also seen in a patient with a tumor not involving the frontal lobes (Bucy, 1931). Gelmers (1983) demonstrated on CT scan a lesion in the supplementary motor area (SMA) in a patient with a strong contralateral grasp reflex. However, De Renzi and Barbieri (1992) found the cingulate gyrus damaged in 70%, and the SMA in only 26% in 44 patients with grasping reflexes. In a prospective study on 491 brain-damaged patients 8% had a grasp reflex. The locus was either frontal or in the deep nuclei and subcortical white matter. The reflex never occurred in retrorolandic lesions.

The disinhibition rate of the grasp reflex was not very high in dementia or diffuse cerebral dysfunction, reaching a maximum of about 45% in 'organic brain syndrome' and 38% in chronic schizofrenia (Villeneuve et al., 1974), and 40% in Parkinson–dementia (Pearce, 1974; Paulson and Gottlieb, 1968).

Jenkyn et al. (1977) found an association between the grasp reflex and 'diffuse cerebral dysfunction'. Tweedy (1982) did the same findings. In both studies the percentage of disinhibition of the reflex was low: 12% resp. 15%. Koller et al. (1982) could not confirm these findings; only 2 out of 52 Alzheimer patients showed the sign. The findings of Lohr (1985) of grasp reflexes in two otherwise healthy patients with schizofrenia may cast new light on the reports on frontal deficits in schizofrenia. In the alien hand syndrome, a constellation of deficits of upper extremity motor control attributed to dysfunction in the SMA/mesiofrontal region, the grasp reflex was often present (Banks et al., 1989; Gasquoine, 1993)

The grasp reflex may be the most 'frontal' of the primitive reflexes. The assumption that almost all PR are of frontal origin is not supported by the fact that the prevalence of these signs, except the grasp reflex, does not increase after frontal leukotomy (Benson and Stuss, 1982). A (persisting) grasp reflex is considered to be the consequence of contralateral frontal damage.

2.2.4 Grasp reflex, plantar (GrPl)

Synonyms	Toe–grasp, tonic foot reflex (Plantaire grijpreflex)
Elicitation and response	Pressure to the ball of the foot causes curling of the toes.
First description	Barraquer (1921) cited by Wartenberg (1945); Schuster (1923)
Core reference	Botez and Bogen, Acta Neurol Scand (1976)

Schuster and Pinéas (1926) found the reflex in three patients with a right–sided hemiplegia. They did not attribute the sign to a circumscribed lesion, but supposed a disturbance in the constellation of different 'aggregates' of the motor system and its conducting system. According to Wartenberg (1945) this sign was caused by a decrease of cerebral inhibition. It consists of a rather slow movement and it has to be distinguished from the Rossolimo reflex, which is a rather brisk movement. The reflex was considered the counterpart of the palmar grasp reflex. Botez and Bogen (1976) found the reflex and related phenomena following cerebral commissurotomy, without any other abnormalities. The reflexes appeared to be facilitated by a standing or sitting position. The grasp reflexes were more marked on the side of the more damaged hemisphere. Hanson and Jones (1989) wrote a review on the tonic foot response and its sequelae in cerebral palsy.

The conclusions and some of the findings are basically the same for the plantar and for the palmar grasp reflexes. The plantar grasp reflex has by far not been studied as extensive as its palmar counterpart.

2.2.5 Head retraction reflex (HeRe)

Synonyms	mediofacial, faciocervical, neck stretch reflex (Hoofdretractie- of neuspunt-hoofdschud-reflex)
Elicitation and response	Tapping the upper lip causes a backward jerk of the head.
First description	Nemlicher et al. (1931)
Core reference	Wartenberg, Amer J Med Sc (1941)

The first author, using the first synonym's name, considered it a periostal reflex. The reflex was present in patients with various diseases, as pseudobulbar palsy, ALS, and in bilateral hemiplegia. Nemlicher considered it a pathognomonic sign of high bilateral damage of the pyramidal tract. Förster (1936) found that tapping on any part of the face could elicit the reflex. Wilson (1940) claimed to be the first author; however, the first part of his book dates from 1932, which is one year after Nemlicher's publication. Wartenberg (1941; 1945), who was the first to use the present name, found it while he was trying to elicit a snout reflex in an ALS patient. The HeRe can sometimes be the only sign of a supracervical localization in a pyramidal lesion. It was found quite frequently in ALS, cerebrospinal lues, and hypertensive encephalopathy. Wartenberg considered the HeRe as a myotatic disinhibition sign. Sandyck et al. (1982) found the HeRe present in 17.2% of Parkinson patients, 8% of patients with senile dementia, and in 4.9% of normal controls. There was a correlation between the presence of the reflex and the severity of Parkinson's disease, suggesting a relation between the disease process and the reflex. Sandyck thought that the HeRe might help distinguish Parkinson's disease (PD) from dementia with extrapyramidal signs.

The HeRe may be considered as an unspecific disinhibition sign of a bilateral lesion in the pyramidal tract. There appears to be no reason to suppose a special relationship with PD.

2.2.6 Mouth open finger spread reflex (MOFS)

Synonyms	Schnapp-Krall or -Strahl reflex (Mondopen-vinger-spreidreflex)
Elicitation and response	Wide opening of the mouth causes spreading of the fingers.
First description	Gött and Dräseke, independently in 1921
Core reference	Alberts, Nervenarzt (1955)

Darwin (1877; quoted by Alberts, 1955) already observed spreading of the fingers; he considered it as 'body language', an expression of surprise. Dräseke saw the reflex as a normal phenomenon in school children. Gött supposed it was the expression of the wish for cooperation of the children he examined. Alberts (1955) examined thousands of children aged 6, 10, and 12–14 years old. The prevalence of the sign decreased with age, from 79% to 43%. Girls, nervous children and children from a rural area showed the MOFS somewhat more often. In 66% the sign was found bilaterally; if not, the right MOFS prevailed. The 10% left-handers showed the reflex stronger or more often on their left side. The sign tended to appear slightly less frequent in the pupils that were considered to be less intelligent. Alberts' explanation for his findings is directed towards a phylogenetic theory. Rennertz (1956) followed a similar explanation for a 9 year old girl that had a MOFS. Touwen (1970) described the reflex in children and devised a scoring scale. He considered the MOFS as a normal sign from the age of 3 years; its prevalence should decrease gradually. A persisting MOFS from the age of 9 should be considered a sign of retardation in motor development. The clinical significance in adults is unclear, since reports on this reflex in adults are scarce. It has been related with diffuse hemispherical disease and it was seen in four generations in one family (Bronisch, 1979).

2.2.7 Nuchocephalic reflex (Nuch)

Synonyms	– (Nuchocephale reflex)
Elicitation and response	Turning the shoulders to one side is followed by the head.
First description	Jenkyn (1975)
Core reference	Jenkyn et al., J Neurol Neurosurg Psychiatry (1975)

Jenkyn et al. described and evaluated this reflex, initially reporting a 70% correlation between the disinhibited Nuch and cognitive disturbances. These results could not be replicated in a second study, however a 52% (significant) correlation was found (Jenkyn et al., 1977). The neuroanatomic basis for the sign is unknown. The authors hypothesized that it may well be analogous to the oculocephalic reflex, which is disinhibited in hemispherical disease when the brainstem, including the oculovestibular system, is spared. Paulson (1978) mentioned the reflex as a sensitive indicator of early dementia. The disinhibited reflex is present in Alzheimer's and Parkinson's disease, suggesting that inhibiting mechanisms may be impaired by both cortical and subcortical disturbances. However, the findings of Jenkyn et al. in 1985 in which the Nuch was found to be present in 20% of healthy people over 70 years old should be kept in mind.

2.2.8 Palmomental reflex (Palm)

Synonyms	Palm–chin reflex (Palmomentale reflex)
Elicitation and response	Scratching the thenar causes a contraction of the mentalis muscle.
First description	Marinesco and Radovici (1920)
Core references	Dalby, Acta Neurol Scandinav (1970) Martí-Vilalta, Eur Neurol (1984)

The reflex was first found in a patient with ALS; the reflex zone was extended over a wide area of the body, but it was easiest elicited by scratching the thenar. It was considered a pathognomonic sign of a (sub)cortical pyramidal lesions. Blake and Kunkle (1951) noticed a wide variety in the reported prevalence in normal adults from 0-58%.

Reis (1961) found the reflex always present when studied electrophysiologically, so did Ansink (1960, 1962). McDonald (1963) confirmed this, adding that the persistence of the reflex was influenced by the state of anxiety. He and Otomo were the first to standardize the scoring of the sign. The prevalence in healthy people over 60 years was found to be high, but many attempts to correlate the Palm with various neurological disorders failed (Hildenhagen, 1976; Gossman and Jacobs, 1980; Strub and Black, 1981; Koller, 1982). The reflex was considered to be of pathological nature when the reflex was persistent and the reflexogenic area was enlarged by Dalby (1970). A persistent Palm would indicate diffuse cortical degeneration or a lesion in the extrapyramidal tract. The reflex was frequently found in Down's syndrome by Little and Masotti (1974) and Thase (1982). The latter considered the Palm as indicative for dementia. Martí-Vilalta and Graus (1984) found the persistence of the reflex the most important indicator for pathology. Huber and Paulson (1986) found the sign useful as an indicator for the severity of Parkinson's disease. Whittle (1986, 1987) finds the Palm a "neurophysiological curiosity of phylogenetic interest", without diagnostic significance. Mack (1987), in the contrary, finds the Palm higly sensitive for dementia paralytica and an ominous sign in coma patients, when persistent and bilaterally present. In conclusion, it can be stated that the Palm. may be found in many neuropsychiatric disorders, without being an aid in differentiating between various diseases. The utility of obtaining an unhibited Palm is unclear. It is considered neither a specific, nor a sensitive sign. Perhaps, when persistent, it is a clinically useful sign of corticobulbar or corticospinal tract dysfunction, rostral to the caudal part of the pons, in the contralateral hemisphere.

2.2.9. Pollicomental reflex (Poll)

Synonyms	- (Pollicomentale reflex)
Elicitation and response	Scratching the thumb causes a contraction of the mentalis muscle.
First description	Marinesco and Radovici (1920)
Core reference	Martí-Vilalta, Eur Neurol (1984)

Marinesco and Radovici (1920) noticed an extension of the reflexzone of the Palm while scratching the distal phalanx of the thumb. Reis (1961), McDonald et al. (1963), and Martí-Vilalta and Graus (1984) confirmed that the Poll is merely a modification of the Palm. Brakha (1958) studied the reflex extensively and considered it a titration of the Palm, but still a separate entity, indicative for insufficient inhibition by or a lack of maturation of the premotor area (Brodmann 6). Constantinidis et al. (1976, 1985) found the Poll (and the Palm) "fairly common" in patients with Alzheimer's disease. Van Tiggelen (1983) found the Poll useful as an indicator of the development of cortical dementia and vulnerability for delirious reactions in case of physical illness and exposure to potentially psychotoxic medication. In conclusion: the Poll seems to be a variant of the Palm, though some authors apparently do not share this opinion.

2.2.10. Rooting reflex (Root)

Synonyms	turning-to reflex (Tepel-zoekreflex)
Elicitation and response	Touching the corner of the mouth causes turning of the lips / head towards the stimulus.
First description	Pepys (1667)
Core reference	Paulson, in Wells' 'Dementia' (1977)

Pratt et al. (1930) attributed the first description to Samuel Pepys who in 1667 wrote in his diary: "They tell me what I did not know that a child will hunt up and down with its mouth if you touch the cheek of it with your finger's end for a nipple and fits its mouth for sucking".

In babies the rooting reflex normally disappears after ± 2 months. It is associated with the suck reflex and helps in nourishing the newborn. Oppenheim (1903) thought that the reflex was an extension of the sucking reflex. Opening of the mouth as part of the reflex was described by Blanton (1917), Dennis (1934) and by Gesell and Ilg (1937). Bühler and Hetzer (1935) also included in their definition sucking movements of the lips or opening of the mouth. Gentry and Aldrich (1948) found the reflex to be absent in sleeping children. Denny-Brown (1956) called the sign the "turning-to reflex", and supposed it to be of frontal origin. Prechtl (1977) expanded the elicitation area to the upper and lower lip.

The rooting reflex was not found by Jenkyn et al. (1977) in 75 adult patients with diffuse cerebral dysfunction. Tweedy et al. (1982) examined 103 subjects including 12 with Parkinson's disease. Only one patient manifested a rooting reflex. Tweedy et al. and Paulson (1977) concluded that, though rare, this reflex may be of clinical use only in terminal phases of dementia.

Minderaa (1985) described visual rooting reflexes in autistic individuals. This reflex was elicited by slowly approaching the subject's face with a waving reflex hammer. Any forward movement of the head in the direction of the object, as if to touch it and protrusion or opening of the mouth was noted.

In conclusion, the Root seems to be present in adults only in the end stages of dementia, when many cerebral systems are dysfunctional. It cannot be used as a predicting or localizing sign.

2.2.11 Snout reflex (Snout)

Synonyms	orbicularis oris, lip, Rüssel-, Schnauzen-reflex, réflexe buccal, de la trompe, de la moue, profond de l'orbiculaire oral (Snoutreflex).
Elicitation and response	Tapping the upper lip causes protrusion of the mouth.
First description	Escherich (1898) in the infant; Toulouse and Vurpas (1903), and Bechterew (1903) in adults.
Core references	Tweedy, Neurology (1982) Girlanda, Eur Neurol (1986)

Escherich, while studying the Chvostek-phenomenon, found the snout reflex in a healthy neonate. Bechterew described the reflex in adults with dementia paralytica. Toulouse and Vurpas ascribed the sign to a cortical dysfunction due to various diseases. Wartenberg (1941) considered it a sign of a corticobulbar lesion in the neonate.

Ekbom (1952) and Ansink (1960) found the snout reflex electrophysiologically always present in adults; an early unilateral and late bilateral response was distinguished. The sign was amplified or asymmetrical in pyramidal injuries rostrally to the facial nucleus. Girlanda et al. (1986) found similarities with the blink reflex, concerning facilitation of the R2 response in parkinsonians and augmentation of the R1 in pseudobulbar palsy.

Brakha (1968) found the reflex absent in 2200 normal adults and present in lesions in the frontal lobe. He considered it highly specific for antero-mediobasal forebrain injury. The snout reflex was found to be disinhibited in 19-65% in various other series. Paulson and Gottlieb (1968) found a 52% presence in a series of 85 demented patients, with a mean age of 62. Villeneuve et al. (1974) scored 22-79% in four different patient groups, from schizophrenia to senile dementia. The mean ages of the patients was high, ranging from 71-83 years. Jenkyn et al. (1977) found the sign in 40% in diffuse cerebral dysfunction; a correlation was demonstrated between cognitive decline and the snout in combination with other signs. Tweedy et al. (1982) confirmed this, adding a 50% presence in Parkinson patients; he found a correlation between ventricular enlargement and the snout reflex. However, Koller et al. (1982) found no correlation beteen the snout reflex, cerebral atrophy and cognitive decline. According to Jacobs and Gossman (1980) there was no difference in the prevalence of the sign in normal controls and parkinson patients. They attributed its presence to normal aging. Isakov et al. (1984) found the snout reflex, if not present in combination with two other signs, of no diagnostic value in patients with prolonged coma and with hemiplegia; the prevalence of the reflex did not differ from age-matched controls. Minderaa (1985) reported that the snout reflex was significantly more prevalent in patients with infantile autism (mean age 19.5) than in age-matched controls.

With the exception of Bracha, most authors consider the snout reflex as a rather unspecific sign, related to diffuse cerebral dysfunction. However, it is present in normal aging as well.

2.2.12 Suck reflex (Suck)

Synonyms	Fressreflex (Zuig-reflex)
Elicitation and response	Touching the lips causes sucking.
First description	Oppenheim (1903)
Core references	de Ajuriaguerra, Encéphale (1963)
	Delwaide, l'Actualité en Gérontologie (1980)

The probably first description of a suck reflex in an adult was in a patient in an epileptic coma. This sign may be present in an anencephalic newborn or in a locked-in state, indicating a brainstem localization for afferent input and motorresponse, the reflex thus being independent on the forebrain.

In adults, the suck reflex was described by many authors as a sign of diffuse cerebral dysfunction (de Ajuriaguerra et al., 1963; Villeneuve et al., 1974; Jenkyn et al., 1977; Estañol, 1981; Delwaide and Dijeux, 1980; Constantinidis and Richard, 1985; Backchine et al., 1989; Franssen et al. 1991). In the French–Swiss literature it is considered to be of value as a localizing sign for temporal lesions. Jenkyn and Reeves (1984) consider the suck reflex basically similar to the snout reflex. This vision is not supported by others, for instance Franssen et al. (1991). They consider the suck reflex to be a prehensile sign, showing up in the late stages of dementia, whereas the snout reflex is a nociceptive sign, which tends to appear in the early stages of dementia and to gradually diminish when cognitive functions decrease.

In conclusion, the suck reflex seems to be a sensitive sign for diffuse brain disorder. The question remains whether it has any localizing value.

2.2.13 Support reflexes, palmar (SuPa)

Synonyms	- (Palmaire steunreflex)
Elicitation and response	Dorsiflexion of the hand causes extension in the elbow.

For discussion see section 2.2.14.

2.2.14 Support reflex, plantar (SuPl)

Synonyms	- (Plantaire steunreflex)
Elicitation and response	Dorsiflexion of the foot causes extension in the knee.
First description	Magnus and Rademaker (1931)

The palmar and plantar supporting reflexes are well-known in child neurology. However, both reflexes have seldom been examined in adults. The (positive) supportreflex is the static modifiation of the spinal extensor thrust, described by Sherrington (1947) as a short lasting extensor-reaction, which was elicited by a sudden pressure under the ball of the foot. The reflex has been considered of spinal origin. However, Twitchell (1965) and Bobath (1971) found support reflexes in patients with bulbar and hemispherical damage. They are used in physiotherapy of the hemiplegic patient as a diagnostic and therapeutic tool (Kollen, 1982). The reflexes have been described in patients after commissurotomy and with multiple sclerosis (Botez and Bogen, 1976; Franklin et al., 1989). The clinical significance of the reappearance of these signs in adulthood is far from clear as yet.

3 Primitive reflexes in healthy, adult volunteers and neurological patients: Methodological issues

This chapter is in press in its present form as journal article:
Vreeling, F. W., Jolles, J., Verhey, F. R. J., & Houx, P. Primitive reflexes in healthy, adult volunteers and neurological patients: Methodological issues. *Journal of Neurology*.

3.1 Summary

The literature on the prevalence and clinical value of primitive reflexes (PR) in adults is inconclusive and confusing. This is due to a lack of standardization of methods to elicit and score these reflexes. Furthermore, instructions to the subject and the investigator and data on inter– and intraobserver reliability are often inadequate or absent. The aim of this study was therefore to find out: 1. Do two experienced clinicians elicit and score PR differently? and 2. Can reliability be improved by standardization? Three studies were carried out, using a protocol for the examination of 14 PR. In the first study with 31 healthy young subjects, two investigators found virtually no difference in the routine neurological examination. However, the interobserver agreement was very poor, indicating the need for a further improvement of the PR protocol. In the second study, 30 neurological patients were examined with an improved, more explicit and standardized protocol, in which the amplitude and the persistence of the reflex were scored separately. Interobserver agreement improved considerably, and was high for amplitude as well as persistence. In the third study, 36 neurological patients were examined twice by one investigator within two weeks. Good to excellent intraobserver agreement was found. No pathognomonic or strictly localizing reflex could be distinguished.

3.2 Introduction

Adult neurological patients sometimes exhibit a number of neurological reflexes that are also present in the earliest stages of ontogenetic development. These developmental, or primitive, reflexes (PR) are ubiquitously present in fetal life, in the newborn and in infants, and gradually disappear with increasing age. It is hypothesized that PR in mature subjects represent release phenomena, reflecting a decrease in higher cortical control over lower centers. According to this hypothesis, reflexes existing in early stages of ontogenesis are suppressed as the brain matures, but may reappear in old age when cerebral inhibition decreases: "once a man, twice a child" [1,2,36,51,52].

The clinical value of PR in adults has not been established. There have been claims for various PR to be pathognomonic for diseases such as Parkinson's disease [26,57] or dementia [37,59,61]. Several authors have argued that particular PR may be indicative of the cerebral location involved. Diffuse hemispherical damage or focal, notably frontal, lesions have been mentioned in this respect [6,9,12,54,63]. Some authors have claimed that there is a relation between PR and specific neuropsychological dysfunctions and the degree of cognitive deterioration [7,13,21,25,37,56]. Others question the value of PR in a routine neurological investigation, arguing that PR have no specific diagnostic value but are merely a sign of physiological aging [19,29,33,39,40]. The literature on the possible clinical relevance of PR is thus inconclusive and unclear.

A major problem when comparing various studies on PR is that the values given for the prevalence and incidence of these signs vary among the research papers. One important reason for this may be the lack of standardization in how these reflexes are elicited [21]. The circumstances under which the reflexes are elicited are usually not described and seldom applied in a standardized fashion. If a description is given, it is often too concise and may differ from author to author. Moreover, it is not clear what, if any, instructions are given to the subject [37,62]. Another problem is that investigators also differ in the interpretation of particular reflexes and their scoring, with research papers showing diversity in the assessment in quantitative terms. For instance, Otomo [50] did not evaluate the palmomental reflex as positive when fewer than 5 successive contractions were found. Others, using less strict criteria, found a greater prevalence of this reflex in normal subjects [8,45]. Several authors suggested that the intensity and/or the persistence of the response, i.e., the lack of habituation, might be of more significance than its mere presence [20,25,42,47]. A third problem is that the PR examined vary from study to study, and it is not often that more than one or two PR are investigated. A 'primitive reflex profile' for a broad range of signs has been established in child neurology [4,14,15,48]. However,in adult neurology, it is only recently that such a PR profile, including a scoring system, has been described [25]. Lastly, there is little information about interobserver and intraobserver reliability, even though the need for it is well recognized [35,36,48,61,62].

The aims of the present study were to find out 1. to what extent clinically experienced neurologists agree in their method of eliciting, assessing and scoring a PR profile, and 2. whether this agreement can be improved by devising and applying a semiquantified and systematized battery of PR. Three studies were carried out. In the first study interobserver reliability was examined for 14 PR examined in 31 young, healthy volunteers. The second study examined *inter*observer reliability for a standardized, semiquantified battery of 14 PR applied to 30 neurological patients. In the third study *intra*observer reliability was examined for the same battery applied to 36 patients.

Table 3.1. Primitive reflexes studied – Abbreviations.

	Nociceptive	
1.	Glabellar tap reflex	Glab
2.	Head retraction reflex	HeRe
3.	Palmomental reflex	Palm
4.	Pollicomental reflex	Poll
5.	Snout reflex	Snout
	Prehensile	
6.	Grasp reflex, palmar	GrPa
7.	Grasp reflex, plantar	GrPl
8.	Rooting reflex	Root
9.	Suck reflex	Suck
	Remainder	
10.	Asymmetric tonic neck reflex	ATNR
11.	Mouth open finger spread reflex	MOFS
12.	Nuchocephalic reflex	Nuch
13.	Support reflex, palmar	SuPa
14.	Support reflex, plantar	SuPl

The battery chosen for the studies consisted of PR of the following three categories (see table 3.1 for the list of PR and abbreviations). In the first place, reflexes were taken that are often mentioned in relation to brain abnormalities in adults and/or aging persons. The glabellar tap [32,38,51,65], palmar grasp [27,34,54,58], palmomental [8,20,45,50], rooting [7,22,25], snout [2,10,22], and suck [2,7,18] reflexes are in this category. A second category consists of PR that are not frequently used, but which are mentioned by particular authors in relation to brain aging and brain abnormalities. The head retraction [5,49,57,63], nuchocephalic [37,51], and pollicomental [12,47] reflexes are in this category. The third category consists of PR used in child neurology and which are potentially useful in adults: the asymmetrical tonic neck reflex (ATNR) [4,14,43], plantar grasp [9,15,24,46], mouth open finger spread (MOFS) [3,30,60], and palmar and plantar support [4,9,15,46] reflexes are in this category. The order in which the PR are listed in table 3.1 is in accordance with, and an extension of, proposals made by Franssen et al. [25]. Reflexes nrs. 1-5 are in the category of 'nociceptive' signs, reflexes nrs. 6-9 are 'prehensile' signs, and reflexes nrs. 10-14 are categorized as 'remaining' reflexes. The reasons for this categorization are discussed elsewhere [25,62].

3.3 Study I: Primitive reflexes in 31 healthy volunteers

3.3.1 Introduction

The purpose of the first study was to investigate the agreement between investigators in how they elicited, assessed and scored PR in healthy young volunteers. Two experienced clinicians discussed the above-mentioned PR extensively. A protocol for the examination of 14 PR was devised, consisting of a description of the position (supine or upright) of and the instructions to the subject (e.g., "relax, close your eyes"), the stimulus, the response, and the scoring. The place and nature of the stimulus and the response were described. Where more than one possible method was given in the literature, the most widely used method was taken.

A three-point scoring system was used to classify each reflex as absent (0) or present (1 or 2). The amplitude of the reflex was differentiated in terms of weakly-moderately present (score 1), and strongly present (score 2). In those cases where persistence was scored, reflexes were considered as (present but) not persistent after 1–4 consecutive responses (score 1); a reflex was scored

Table 3.2. Example of description of reflexes as used in study 1.

Snout reflex:

Basic Position:	Subject is supine.
Instruction:	Relax and keep your eyes closed.
Stimulus:	Slight tap on the middle of the relaxed, closed mouth
Response:	Protrusion of the lips.
Scoring:	0: no response
	1: protrusion, less than 4 consecutive responses
	2: protrusion, 4 or more consecutive responses

persistent after 4 or more consecutive responses (score 2). The glabellar tap and the nasopalpebral reflexes were considered to be present but not persistent after 4-10 consecutive responses (score 1), and to be persistent after more than 10 consecutive responses (score 2). This is in accordance with the literature [26,33,36,51–53]. If appropriate, the reflex was elicited on both sides. The description of the snout reflex in table 3.2 serves as an example for the entire battery.

3.3.2 Material and Methods

Subjects. Thirty-one healthy volunteers were used for this study. The age ranged between 21 and 25 years (mean age 22; 20 females/11 males). Twenty subjects were medical students, and 11 subjects had responded to an advertisement placed in a local newspaper. All subjects were told about the aims of the study and informed consent was obtained. Subjects were paid for their participation. The choice of young volunteers was based on the argument that it would be necessary to ask the subjects for possible differences in how the reflex was elicited by the two neurologists in order to be able to construct an optimal and standardized battery of PR.

The protocol. A complete medical history was taken and a routine medical examination was performed. Each subject was given a thorough neurological examination and the entire battery of 14 PR by two experienced clinicians. The results were independently noted on a standard form.

Procedure. Subjects were told about the investigation two at a time. The protocol was then carried out by each of the investigators. Fifteen subjects were examined first by investigator 1 (third author) and then by investigator 2 (first author); 16 subjects were examined in the reverse order. Care was taken not to influence the subjects by providing information that might interfere with the response pattern.

3.3.3 Results and discussion

The IOR was measured for the neurological examination, the various PR separately, and for the total reflex battery. Table 3.3 shows the results for the two investigators separately. The agreement in terms of the presence or absence of the reflex, and the agreement on the amplitude or the persistence of the response are given. The total results for the entire battery are also shown.

The majority of the PR were scored as not present, as expected for a group of young, healthy subjects [33,52]. The head retraction, rooting, suck, ATNR, and palmar and plantar support reflexes were never rated positive by

Table 3.3. Scores by two observers for reflexes in study 1.

		Observ. 1 score		Observ. 2 score		Agreement		score	
Reflex		1	2	1	2	abs.	pres.	1	2
Glab		1	1	4	2	23	0	0	0
Palm	L	2	1	3	0	25	0	0	0
	R	1	4	3	0	23	0	0	0
Poll	L	1	1	1	0	28	0	0	0
	R	1	1	2	0	28	1	1	0
Snout		0	0	4	0	27	0	0	0
GrPa	L	0	0	6	0	25	0	0	0
	R	0	0	6	0	25	0	0	0
GrPl	L	0	0	1	0	30	0	0	0
	R	0	0	1	0	30	0	0	0
MOFS	L	0	0	0	0	31	0	0	0
	R	0	0	2	1	28	0	0	0
Nuch	L	1	0	0	0	30	0	0	0
	R	1	0	0	0	30	0	0	0
TOTAL		8	8	33	3	724	1	1	0

Note: The asymmetric tonic neck reflex, the head retraction, rooting, suck, palmar and plantar support reflexes were not found by either of the observers.

either of the investigators. On the other hand, the glabellar tap, the palmomental, and the pollicomental reflexes were found by both investigators. However, there was a lack of agreement between the two investigators with respect to the subjects showing a positive response, as is evident from table 3.3. Furthermore, particular reflexes were found exclusively by investigator 2, namely the snout, the palmar and plantar grasp reflexes, and the MOFS. The nuchocephalic reflex was found only once by investigator 1. There was another systematic difference in that investigator 2 found more than twice as many positive responses as investigator 1. With respect to the assessment of 'intensity': investigator 1 scored seven reflexes as 'strongly present' and one as 'persistent'; investigator 2 scored one reflex as 'strongly present', and one as 'persistent'. There was no agreement on the intensity assessment.

A remarkable finding is that 29 out of the 52 positive scores (56%) involved three reflexes, namely the glabellar, palmomental and pollicomental reflexes. For all reflexes there was agreement between the two investigators in 724 out of 775 observations, in that the reflex was not present. However, agreement about a reflex being present was found for only 1 out of 52 observations.

After all subjects had been examined and independently assessed, the investigators discussed the results. The instructions to the patient, their positioning and the way of eliciting a reflex still appeared to be slightly different, due to insufficient description or different interpretation of the protocol. Scoring especially appeared to be a source of error. One investigator tended to score more responses as 'present' than the other. A persistent, but weak response thus could be scored as a '2' by one and as 'absent' by the other investigator. A clear, but single response could also give rise to a different score.

Qualitative information concerning differences between the two investigators was obtained from the 31 subjects after the second neurological examination. They were questioned about 1. the order in which the reflexes were investigated; 2. the way, especially the intensity, in which the stimulus was given; 3. particular instructions given to the subjects. Systematic differences appeared to exist between the two investigators. Firstly, the investigators differed in the sequence in which they examined the reflexes. One investigator followed the standing, sitting, and supine position; the other followed the physical region that was involved in eliciting the reflex. Secondly, the stimuli presented by investigator 2 were stronger, according to all subjects. In some cases reflexes were elicited differently. Lastly, investigator 1 requested subjects to close their eyes more often than investigator 2.

The results of this study showed that most reflexes were not present in this group of healthy volunteers, and that the two neurologists agreed with each other in this finding. However, there was only one case in which both investigators scored a reflex as being present; this is extremely low, even if the small number of positive findings is taken into account. There are several possible explanations for these findings. One possibility is that "a bottom effect" plays a role: because positive reflexes are not very probable in these healthy subjects, an investigator is stimulated to pay more attention to slight motor changes which would not have attracted attention under normal clinical conditions. This makes positive scores rather dubious. The problem then arises if a trivial, but persistent motor change should be scored more than or different from one clear, but single response. This suggests that still more effort should be put into carefully describing a response, including a separate description of amplitude and persistence. A second possibility is suggested by the qualitative information given by the subjects after the examination, namely that there were differences between the two investigators in how they elicited reflexes. This indicates that the instructions for the investigator should also be improved. The next study was performed with such an improved methodology.

3.4 Study 2. Interobserver reliability in 30 neurological patients

3.4.1 Introduction

The low IOR found in study 1 is of relevance because it was performed by two experienced clinicians using an explicit and standardized PR protocol. This is of interest as the majority of scientific papers on the possible clinical value of PR do not give any information about IOR [10–12,40,51,61]. Reports in which IOR was measured give only part of the relevant data. For instance, the results of Jenkyn et al. [36] were obtained for a population which was much younger than the target population in that study (senescence), while only results were given for combined scores over all data. Moreover, no correction for agreement due to chance was applied. A second methodological flaw of many research papers on PR is that the description of how PR are elicited and the scoring criteria is too general [1,36,40]. Together with the findings of study 1, which suggested that there was virtually no agreement between the investigators, these findings indicate that reports on the prevalence of PR in healthy subjects should be interpreted with caution. It is therefore essential to describe how reflexes are elicited and scored still more explicitly, to enable reliable statements to be made as to the presence or absence of PR in various patient groups and healthy elderly subjects.

A revised battery of primitive reflexes (BPR) was prepared on the basis of experience gained in study 1 and the points raised above. It was tested on a heterogenous group of 30 hospitalized neurological patients. The patients covered various major neurological diseases, so as to increase the possible prevalence of PR in this group and thus enable a better investigation of interobserver reliability.

The PR protocol. The following adaptations were made to the PR protocol. The basic position was described in detail, including closure or opening of the eyes, position of the hands, etc. Then instructions for the subject as to what was expected of him/her (e.g., sitting or standing, eyes open or closed, etc.) and what stimulus was to be expected; this was done in order to prevent possible startle reactions, which might influence the response. No information was given as to the nature of the expected response. Every reflex was measured at least three times, with about two seconds between every elicitation, except for the glabellar tap and the nasopalpebral reflexes, which were elicited ten consecutive times at two times per second. A detailed description is given for each reflex separately.

Scoring. All reflexes elicited in the battery of PR (BPR) were judged on the criteria of amplitude and persistence. A three-point scale for both characteristics was used. For amplitude 0= absent, 1=weak to moderate amplitude, and 2= strong amplitude. A well-defined description of the responses with weak-moderate and strong amplitudes was given for each reflex separately. For persistence 0= absent, 1= <4 consecutive responses (present, but not persistent), and 2= at least 4 consecutive responses (persistent). The glabellar tap and the nasopalpebral reflexes were considered to be present, but not persistent after 4-10 consecutive responses, and persistent after more than 10 consecutive responses, in accordance with the literature [31,33,51–53].

Thus, each reflex was scored with a two cipher code, the first cipher being for the amplitude and the second for the persistence. For instance, score 1.2 means that a certain reflex showed a weak-moderate amplitude, and that it

Table 3.4. Example of how reflexes were elicited and scored in study 2 and 3.

Snout reflex:

Basic position:	Subject sits up straight; the eyes are closed.	
Instruction:	Keep your mouth loosely closed and your eyes closed. I will tap your lips a few times with my hammer.	
Stimulus:	Slight tap on the middle of the lips with a reflex hammer	
Response:	Amplitude	0:no response
		1:phasic protrusion of the lips
		2:tonic protrusion of the lips, with or without extension of the reflex response.
	Persistence	0:no response
		1:< 4 consecutive responses
		2:≥ 4 consecutive responses

was persistent. The reflex was scored negative (0.0) for both amplitude and persistence, respectively, when no response was found three times in succession. A negative score for a particular reflex was not changed when the response was found positive after another stimulus (e.g., a grasp reaction measured upon stimulation for the palmomental reflex). The scoring was conservative: any doubt as to the presence would result in a score 'not present'. Table 3.4 describes the revised protocol for the snout reflex. The revised protocol for the BPR is available on request to the first author.

3.4.2 Material and methods

Subjects. A heterogeneous group of 30 hospitalized neurological patients was used for the examination. All had given their informed consent. The age of the subjects ranged from 17 to 84 years (mean 59, 11 females/19 males). They were in a stable medical and neurological condition. Thirteen subjects had a diagnosis of stroke; five patients had one or more infarctions in the right hemisphere, and eight patients had one or more infarctions in the left hemisphere. Three patients were considered to have vascular dementia, and five patients had diseases of the spine. The rest of the patients had received the following diagnoses: vasculitis, brain tumor, multiple sclerosis, anosmia, muscular dystrophy, cerebrovascular problems, headache, brain trauma and brain atrophy e.c.i..
Statistics. The interobserver reliability (IOR) was estimated by Cohen's kappa [16,23], which corrects for agreement due to chance. A weighted kappa (K_w) was used, following Cicchetti's proposals [17] for assessing the reliability of a dichotomous-ordinal rating scale (i.e. a scale containing a point of absence and two (or more) points of presence); K_w was computed for all separate reflexes. Kappa values between 0.4 and 0.6 were considered 'modest'; kappa values between 0.6 and 0.8 were considered 'good', and values above 0.8 were judged 'very good'[41]. Z-scores were computed for every kappa. Z–scores of 1.65 or more indicate a probability of $p< 0.05$ (denoting statistical significance), and Z-scores of 2.33 or more indicate a probability of $p< 0.01$.
Procedure. The patients were examined by the two investigators, using the (revised) BPR, within 24 hours. The circumstances as to resting hour, food intake, and place of examination were the same for both examinations. Both investigators elicited the reflexes in the same order. The reflexes elicited in a standing position were tested first, followed by those elicited in a sitting position. Reflexes elicited in the supine position were tested last. This sequence was chosen for patient comfort. Half of the subjects were investigated in the order neurologist 1- neurologist 2, and the other half were investigated in the reverse order.

3.4.3 Results and discussion

The IOR was measured for the various PR separately and for the total reflex battery. Tables 3.5 and 3.6 give the results for amplitude and persistence, respectively, for the two investigators separately. In addition, the agreement in terms of presence or absence of a reflex, and the agreement on the intensity of the response (score 1 or 2) are given. Finally, the total scores for PR are shown.

The glabellar tap, the palmomental, the pollicomental, and the snout reflexes were found quite often by both investigators. Positive responses were rare for both grasp and nuchocephalic reflexes, and the rooting reflex was scored positive and persistent only once by investigator 1. The ATNR, the head retraction, and the plantar and right palmar support reflexes were never scored positive by either of the two investigators.

There was a good correspondence (K_w above 0.6) between both investigators for the amplitude of glabellar, pollicomental (right), snout, plantar grasp, suck, MOFS, and right nuchocephalic reflexes, and a modest K_w for the left pollicomental and palmar grasp, and for the palmomental (right K_w = 0.38) reflexes. However, because of the low numbers of positive responses, the Z-scores for the left palmar and plantar grasp and the right nuchocephalic were clearly too small for the level of significance; the MOFS and plantar grasp on the right nearly reached a the level of significance. A quite similar picture emerged for persistence, with the exception of a good and significant agreement on the plantar grasp and the MOFS on the right. A slight systematic difference was found between the investigators in that investigator 2 found somewhat more positive palmomental and pollicomental reflexes than investigator 1; the greater number of positive observations scored by investigator 2 was almost entirely for these two reflexes.

With respect to the total amplitude score 31 out of the 181 combined observations of both investigators were scored as 'intense' (score 2). There was agreement on 8 cases, (i.e., 16 out of the 31 assessments), indicating that there were 15 cases on which the investigators did not agree (K= 0.67). Scores for persistence appeared to be considerably higher than those for amplitude: 156 out of 185 observations were given a score 2. A high correlation was found between the investigators: they agreed in 58 cases (i.e., 116 assessments; K= 0.70).

The good correspondence between the two investigators with respect to presence or absence, amplitude and persistence of the various reflexes shows that the systematized PR protocol made it possible to collect reliable data. This was especially so for those reflexes that had a high prevalence in this group. The reflexes that were not found or only in a limited number, could not be evaluated for interobserver reliabilty by kappa statistics, or had Z-scores that

Table 3.5. Scores by two observers for reflexes in study 2: Amplitude.

			Obs. 1		Obs. 2		Agreement					
			score		score				score			
Reflex		N	1	2	1	2	abs.	pres	1	2	Kw	Z-score
Glab		29	10	0	12	0	17	10	10	0	0.85	4.36
Palm	L	30	6	0	14	0	16	6	6	0	0.44	2.34
	R	30	7	0	13	0	14	6	6	0	0.38	2.00
Poll	L	30	1	6	1	12	17	7	1	6	0.49	2.49
	R	30	6	0	8	0	21	6	6	0	0.74	3.16
Snout		30	16	0	13	0	13	12	12	0	0.67	3.70
GrPa	L	30	1	1	0	2	27	1	0	1	0.52	1.06
	R	30	3	0	0	0	27	0	0	0	-	–
GrPl	L	26	1	0	2	0	24	1	1	0	0.65	1.16
	R	25	3	0	3	0	21	2	2	0	0.62	1.61
Root	L	30	0	1	0	0	29	0	0	0	-	-
	R	30	0	1	0	0	29	0	0	0	-	-
Suck		30	4	4	7	2	21	8	3	1	0.80	3.70
MOFS	L	17	4	0	4	0	13	4	4	0	1.00	3.09
	R	17	2	0	4	0	13	2	2	0	0.61	1.62
Nuch	L	13	1	0	0	2	12	0	0	0	-	-
	R	13	1	0	2	0	12	1	1	0	0.63	1.16
SuPa	L	29	1	0	0	0	28	0	0	0	-	-
	R	30	0	0	0	0	30	0	0	0	-	-
TOTAL		612	67	13	83	18	497	66	54	8		

Note: The asymmetric tonic neck reflex, the head retraction, and the plantar support were not found by either of the observers. Obs. 1/2 = first en second observer. Kw = weighted kappa

Table 3.6. Scores by two observers for reflexes in study 2: Persistence.

			Obs. 1		Obs. 2		Agreement					
			score		score				score			
Reflex		N	1	2	1	2	abs.	pres.	1	2	Kw	Z-score
Glab		29	2	9	1	11	17	11	1	9	0.90	4.80
Palm	L	30	2	6	1	13	16	8	1	6	0.56	3.04
	R	30	1	8	1	12	15	7	0	7	0.48	2.51
Poll	L	30	1	6	1	12	17	7	1	6	0.56	2.90
	R	30	0	7	0	9	21	7	0	7	0.83	3.66
Snout		30	1	15	1	12	13	12	0	11	0.67	3.79
GrPa	L	30	0	2	0	2	27	1	0	1	0.46	0.96
	R	30	1	2	0	0	27	0	0	0	-	-
GrPl	L	26	0	2	1	1	23	1	0	1	0.74	1.30
	R	25	1	1	2	1	22	2	1	1	0.68	1.76
Root	L	30	0	1	0	0	29	0	0	0	-	-
	R	30	1	1	0	0	28	0	0	0	-	-
Suck		30	3	6	1	5	20	6	1	4	0.72	3.10
MOFS	L	17	1	3	2	2	13	4	1	3	0.94	2.94
	R	17	0	2	1	3	13	2	0	2	0.65	1.75
Nuch	L	13	1	0	0	0	12	0	0	0	-	-
	R	13	1	0	1	2	11	1	1	0	0.53	0.96
SuPa	L	29	1	0	0	0	28	0	0	0	-	-
	R	30	0	0	0	0	30	0	0	0	-	-
TOTAL		612	17	71	13	85	495	69	7	58		

were too low to reach a level of significance with this number of observations. However, the fact that both investigators agreed that a reflex was absent indicates that the BPR with its systematized method of reflex elicitation and scoring can be used with confidence.

3.5 Study 3. Intraobserver reliability in 36 neurological patients

3.5.1 Introduction

The results of study 2 showed that there was a good interobserver reliability (IOR) for all the reflexes tested. This study was performed to address the remaining issue, namely the intraobserver reliability (IAR). For this purpose, 36 neurological patients were examined twice by one neurologist within 10 to 14 days, using the revised BPR.

3.5.2 Material and methods

Subjects. Thirty-six heterogeneous, hospitalized, neurological patients were examined. All had given their informed consent. The age of the subjects ranged from 43 to 91 years (mean 69.2; 16 females/20 males). They were in a stable medical and neurological condition. Fifteen patients had received a diagnosis of cerebral stroke and had one or more cerebral infarctions: 12 in the right hemisphere, 12 in the left hemisphere and 1 in both. Ten patients were suffering from either vascular or Alzheimer's dementia.

Four patients had Parkinson's disease; two patients suffered from a disease of the spine, and the remaining subjects were diagnosed with polyneuropathy, cardiovascular disease, multiple sclerosis, brain tumor and diabetes mellitus.
Primitive reflex protocol and scoring: see study 2.
Statistics: see study 2.
Procedure: One neurologist (first author) applied the BPR twice to each patient, under standard circumstances. The time between the two examinations was between 10 and 14 days. The examiner did not know the patients beforehand and he did not see them between the first and the second examination. The general medical and neurological condition of all patients was stable throughout the whole period of the two examinations; this was controlled by the patient's ward doctor. The scoring forms of the results of the first examination were put away immediately and were inaccessible for the examiner. Only after all second examinations had been carried out, the first

results were taken out and compared with the second results.

3.5.3 Results and discussion

Intraobserver reliability was measured as described in study 2 for interobserver reliability. The pattern of reflexes scored positive or negative was similar as in study 2, as was to be expected in view of the similarity of the patient populations used for the studies. The pattern will not be described in detail here.

As is evident from tables 3.7 and 3.8, there was a good to very good agreement between the two observations, as most kappa values were above 0.8. The rooting and the palmar support reflexes were an exception, their Z-scores being insufficient for significance.

The intensity scores showed a pattern similar to that of study 2. Amplitude was scored as a '2' considerably less often than persistence; 23 observations out of 359 received a score 2 for amplitude. Nearly all these observations were consistent on the two occasions (11 cases, i.e., 22 observations). Persistence was scored '2' in 272 out of 349 observations; again the majority were consistent on the two occasions. There was a very good overall intraobserver reliability, as measured by the kappa value for the battery of reflexes together: K=0.93 for amplitude, and K=0.94 for persistence. As was the case in study 2, kappa statistics could not be applied to those reflexes that were not found at all or only in a limited number. Again, the fact that in both observations there was agreement on their absence indicates that the BPR can be used with confidence.

The results of studies 2 and 3 showed that the improved BPR resulted in a considerable increase in inter- and intraobserver reliability. The BPR can be used for experimental clinical research in adult neurological patients.

3.6 General discussion

Three experimental studies were performed to assess the reliability of elicitation and scoring of PR. We examined the interobserver reliability of two experienced clinicians, using a protocol for the examination of PR based on reports in the literature (study 1). The neurological findings showed perfect agreement, but there was virtually no agreement about the (rare) PR that were found. This indicated the necessity of improving the protocol on various points. The instructions to the patient and the investigator were extended; the way reflexes were elicited was described in more detail, and scoring was sub-

Table 3.7. Scores by one observer for reflexes assessed on two occasions in study 3: Amplitude.

			Occ. 1		Occ. 2		Agreement					
			score		score				score			
Reflex		N	1	2	1	2	abs.	pres.	1	2	Kw	Z-score
Glab		36	20	0	19	0	16	19	19	0	0.94	5.63
HeRe		36	2	0	2	0	34	2	2	0	1.00	2.05
Palm	L	36	17	0	18	0	17	16	16	0	0.83	5.00
	R	36	17	0	16	0	19	16	16	0	0.94	5.63
Poll	L	36	20	0	21	0	14	19	19	0	0.83	4.89
	R	36	20	0	18	0	16	18	18	0	0.89	5.33
Snout		36	27	3	27	3	5	30	27	3	1.00	4.23
GrPa	L	36	2	2	1	2	32	3	1	2	0.88	2.41
	R	36	4	1	3	1	31	4	3	1	0.89	2.79
GrPl	L	36	3	0	2	0	33	2	2	0	0.79	1.82
	R	36	4	0	3	0	32	3	3	0	0.84	2.34
Root	L	36	1	1	1	1	33	1	0	1	0.48	0.99
	R	36	2	1	2	1	33	3	2	1	1.00	2.51
Suck		36	12	3	11	3	21	14	11	3	0.95	5.73
MOFS	L	36	4	0	4	0	32	4	4	0	1.00	2.98
	R	36	5	0	5	0	31	5	5	0	1.00	3.36
Nuch	L	35	5	0	5	0	30	5	5	0	1.00	3.37
	R	35	5	1	6	0	29	6	5	0	0.95	3.54
SuPa	L	36	1	0	1	0	35	1	1	0	1.00	1.43
	R	36	0	0	0	0	36	0	0	0	-	-
TOTAL		861	171	12	165	11	677	169	159	11		

Note: The asymmetric tonic neck reflex and the plantar support were not found on either of the occasions. Occ. 1/2 = first and second occasion. Kw = weighted kappa

Table 3.8. Scores by one observer for reflexes assessed on two occasions in study 3: Persistence.

Reflex		N	Occ. 1 score 1	Occ. 1 score 2	Occ. 2 score 1	Occ. 2 score 2	Agreement abs.	Agreement pres.	Agreement score 1	Agreement score 2	Kw	Z-score
Glab		36	6	13	3	15	17	18	3	13	0.93	6.10
HeRe		36	3	1	1	1	32	2	1	1	0.65	1.75
Palm	L	36	3	14	3	15	17	16	2	13	0.83	5.30
	R	36	3	13	1	15	19	14	1	13	0.96	6.11
Poll	L	36	1	20	2	21	14	33	0	18	0.85	5.22
	R	36	4	15	2	16	16	18	2	14	0.87	5.66
Snout		35	3	27	3	27	5	30	3	27	1.00	4.06
GrPa	L	36	1	3	0	3	32	3	0	3	0.89	2.47
	R	36	1	4	0	4	31	4	0	4	0.91	2.89
GrPl	L	36	2	1	1	1	33	2	1	1	0.82	1.87
	R	36	3	1	1	2	32	3	1	1	0.81	2.21
Root	L	36	1	1	1	1	33	1	0	1	0.58	1.17
	R	36	1.	1	2	1	33	2	1	1	0.82	1.87
Suck		36	5	10	5	9	21	14	5	9	0.96	5.89
MOFS	L	36	1	0	1	0	35	1	1	0	1.00	1.43
	R	36	1	3	2	3	31	4	1	3	0.91	2.86
Nuch	L	35	2	3	2	3	30	5	2	3	1.00	3.35
	R	35	2	3	3	3	29	5	2	3	0.92	3.24
SuPa	L	36	0	1	0	1	35	1	0	1	1.00	1.43
	R	36	0	0	0	0	36	0	0	0	-	-
TOTAL		861	43	133	33	139	675	162	26	119		

divided into a three-grade scale for both amplitude and persistence. This revised BPR was then applied to 30 neurological patients, who theoretically would be expected to show more PR than healthy controls, so that statistics on interobserver agreement would be more reliable (study 2). As was expected, more PR were found. The data on the most prevailing reflexes showed modest to good agreement, as was expressed in moderate-to-high kappa values. The same BPR was applied to another group of neurological patients to test intraobserver reliability. One of the authors examined 36 subjects twice within 10 to 14 days. Again this protocol showed its value by the high kappa values obtained. As for the more rarely found reflexes in both studies, though kappa statistics are not applicable to these low numbers, good to excellent agreement was obtained. This was true for the palmar grasp, rooting, and palmar support reflexes on both sides. Some reflexes were not found at all, i.e., the ATNR, head retraction, and the plantar support reflexes.

The study of the origin, prevalence, and clinical significance of PR in adults has received much attention. As mentioned in the introduction, there are many opinions as to the nature of these signs. It is fundamental to our understanding and knowledge of PR in adulthood to know how often and under what circumstances they (re-)appear. This requires not only sufficient healthy controls and patients with well-defined brain abnormalities in different age groups, but also a standardized protocol for eliciting and scoring PR. Although many authors had sufficient patients (and sometimes controls) in their studies, quite often a methodological description and data on inter- and intraobserver reliability were lacking and the number of PR studied was usually small.

Use of a BPR makes it possible to construct a primitive reflex profile (PRP), as was done by Allen and Capute et al. [4,14,15], and Morgan et al. [48] in child neurology, and recently –to some extent– by Franssen et al. [25] in adults. A PRP may aid our understanding of the clinical value of PR. The reproducibility of the BPR is essential in this respect. However, Franssen did not describe the reproducibility of the reflexes. He used four well defined points to describe the responses, and when in doubt three intermediate numerical scores could be given. However, for some PR the amplitude and for other PR the persistence of the reflex determines the score. Jenkyn et al. [36] evaluated a number of clinical signs in senescence. In the first place, only three PR were examined. Secondly, the interobserver reliability was tested with a younger group of healthy subjects and not with the patient group. Moreover, reliability was expressed in percentages of agreement on positive and negative findings. This could lead to low kappa values, given the expectation of the low prevalence of these signs in this young population. Jacobs and Gossman [33] examined (only) three PR in normal adults of different ages. Their description of how they elicited and scored the reflexes is clear, but they did not provide data on inter- and intraobserver reliability.

The importance of scoring amplitude and persistence separately has been emphasized in the early literature [44]. However, only a few authors have really applied this disctinction to clinical practice. It has been done -to a certain extent- in child neurology [14,15,60]. Capute scored each PR on a five-point scale and required three out of five trials for a particular score. Touwen introduced a three- or four-point score for each PR and stated that 'persistence is a sign of developmental retardation of the nervous system', without grading it. In adults, in three papers on the palmomental reflex [28,42,45] the scoring was more or less separated into amplitude or vividness and persistence. Maertens de Noordhout and Delwaide [42] scored amplitude on a three-point scale, and persistence as present or not (fewer than five successive responses). Martí-Vilalta and Graus [45] followed the same procedure for amplitude, and divided persistence into three categories: 1-4, 5-9, and >9 successive responses. Giménez-Roldán et al. [28] were the only group to use a two-cipher code. The amplitude of a reflex was graded in a four-point scale from 0-4; however, the persistence of a reflex was not graded, but expressed in the number of successive positive responses. Our paper is the first to use a two-cipher grading code to score the amplitude and persistence of PR, which has been applied to patients with Parkinsonism [62] and other neurological diseases.

With respect to the use of kappa statistics, the present results confirm that this method is of great value in clinical research. Its advantage lies in the fact that a correction is made for agreement by chance. The weighted kappa should be applied when a rater scale scale contains a point of 'absence' and two or more degrees of presence, like the present study. The finding of modest agreement on the palmomental and pollicomental reflexes in study 2 is of interest because of conflicting results about these reflexes in the literature. Notwithstanding the elaborate protocol required for these reflexes, the agreement was still less than that found for other PR such as the suck or snout reflex. A posthoc evaluation revealed that investigator 2 used somewhat more force when stimulating the thenar and the distal phalanx of the thumb, which may have increased the prevalence of the response. This interpretation is consistent with the notion put forward by Otomo [50] and by Maertens de Noordhout [42], namely that the discrepancy in the literature can be partly explained by the lack of standardization of the methods used. Of particular importance in this respect is the suggestion of Reis [55] and Paulson [51] that intensive stimulation of the distal phalanx of the thumb and even of the palm always gives rise to a reflex movement of the mentalis muscle. Moreover, McDonald et al. [47] found that the variability of the palmomental reflex was related to the state of emotionality or anxiety of the subject. Taken together, the variability of palmomental and pollicomental reflexes found in the present study with highly standardized methods indicates that other variables may modulate the nature and intensity of the response. Consequently, scores for the prevalence of these two reflexes must be regarded with more caution than those obtained for other reflexes.

In conclusion, experienced clinical neurologists differ in their way of eliciting and scoring PR, even after they have drawn up a protocol. This makes it probable that in other studies there will also be a considerable difference in findings reported by experienced clinicians. These differences may be due to different ways of instructing and positioning the patient, to different ways of administering the stimulus and to a less detailed description of the various aspects of scoring the responses. Thus the great variation in results for PR in comparable patient populations probably stems from the different methodologies used. Past findings should be looked at critically. Investigations on PR in adults should use a protocol that is clear and unequivocal in its descriptions and which leaves as little room as possible for misinterpretation. The improvement obtained in the present paper proves that a meticulously described protocol can indeed lead to well validated results. An explicit, systematized, standardized, and semiquantified protocol is necessary to obtain a satisfactory inter- and intraobserver reliability. The use of kappa statistics is of great value in this respect.

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4 Primitive reflexes in normal aging

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4.1 Summary

Primitive reflexes (PR) have been claimed to reflect a decrease of cortical functioning as observed in Alzheimer's disease or other degenerative diseases and therefore are thought to be pathognomonic for disease processes. However, PR have also been described in normal, healthy individuals, especially in the elderly. To evaluate the relevance of PR for the neurological examination and to establish normative data, the prevalence of 14 PR was examined in 247 healthy adult volunteers with ages ranging from 17 to 83. Also, the effect of rigorous health screening on the prevalence of PR in normal subjects was studied. 97 Subjects had experienced 'biological life events' (BLE; factors associated with brain dysfunctions, other than grossly impairing conditions), and 150 had not. Subjects were assigned to age groups from 20 to 80 years, with or without BLE. PR were assessed following a standardized protocol, in which amplitude and persistence were scored separately. The prevalence of PR increased with age. There was no difference between males and females as to the overall number of PR. Of the young subjects 22% showed at least one PR, for elderly subjects this was 77%. The number of PR tended to increase with BLE, most clearly so with general anaesthesia and use of medicine. In the BLE-affected group some PR showed more often persistence than in the BLE-free group. As many PR occurred not infrequently in normal healthy adults, the relevance of these reflexes can be doubted. The snout reflex, for instance, was elicited in 48% of the elderly subjects. The findings can be used as normative data for the study of PR in adults.

4.2 Introduction

There is an increasing number of studies suggesting that adult patients suffering from dementia or other brain diseases may exhibit a number of neurological reflexes which are also present in the earliest stages of ontogenetic development. These developmental or primitive reflexes (PR, also referred to as 'release signs') are present in fetal life, in the newborn or infant and gradually disappear with increasing age. They may reappear in senescence and with neurological disease. Through the years, there have been claims for various PR to be a pathognomonic sign for conditions such as Parkinson's and Alzheimer's disease[1-3] or to be strictly localizing signs.[4-7]

De Ajuriaguerra et al.[8] hypothesized that PR in mature subjects represent release phenomena, due to a decrease of higher cortical control over lower centers. According to this hypothesis, reflexes that exist in earlier stages of ontogenesis are suppressed as the brain matures, to reappear with diminution of cerebral inhibition: "once a man, twice a child". Following Jacksonian principles of dissolution of the brain, the reappearance of PR would take place in the reverse order in which they developed. Indeed, Delwaide and Dijeux[9] found some evidence in favor of this hypothesis in their longitudinal study of Alzheimer patients; the nociceptive signs (palmomental, snout, glabellar tap) were the first primitive reflexes to develop. In a later stage of the disease the prehensile signs i.e., grasping and sucking appeared. Franssen et al.[10], in their study on Alzheimer patients, found the nociceptive signs to prevail in Reisberg's Global Deterioration Scale[11] (GDS) stages 3–5, whereas the prevalence of the prehensile signs showed a steep increase in GDS stages 6 and 7. However, since it has been demonstrated that primitive reflexes can also be elicited in healthy elderly subjects, the clinical value of PR in a routine neurological investigation has been questioned.[12–17] Already in 1949, Howell[18] found aberrant neurological signs to be common in a group of 200 supposedly healthy male pensioners and warned against making misdiagnoses in the elderly. Hildenhagen's[19] findings were similar. It has therefore been stated that PR have no specific diagnostic value, but are merely a sign of the physiological aging process[20].

A major problem when comparing various studies on PR in adulthood is that the values for prevalence vary among the research papers. One reason for this is the lack of standardization in how these reflexes are elicited and scored. Secondly, some authors consider the intensity of the reflex of importance, others state that the persistence of the response is of more significance than its mere presence. Only in a few studies a score of intensity or amplitude and persistence of the responses have been described[21-23]. Thirdly, PR examined vary from study to study, and often no more than one or two PR are investigated. A 'primitive reflex profile' (PRP) for a broad range of signs has been established in child neurology[24,25]. However, in adult neurology, it is only recently that such a PRP, including a scoring system, has been described[10,26]. Lastly, there is little information about interobserver and intraobserver reliability, even though the need for it is well-recognized[15,27,28].

ably healthy elderly persons, are the consequence of the physiological aging process itself, or that persons exhibiting PR are in any way less healthy than those who do not. In this respect, the concepts of usual versus successful aging are relevant for gerontological studies in all disciplines.[29] Earlier, we described that memory and other cognitive functions were much better in a group of healthy elderly subjects, who had been thoroughly screened for a number of subtle health-related factors, other than grossly impairing conditions such as dementia, brain tumor, etc. (Biological Life Events; BLE).[30,31] Usually, investigators in gerontological studies content themselves with asking their normal subjects whether they are healthy. Studies on PR in the population of retirement facilities may show insufficient screening for health, and the composition of the groups studied is often too heterogeneous for normative data.[16,19,32] Moreover, these studies cannot be regarded as representative for the whole aging population, as the inhabitants of old peoples's homes are likely to be in poorer health then community-dwelling individuals. On the other hand, studies in which a thorough screening of gross health factors has been done lack a description of the elicitation and scoring of the PR.[17,38]

The present study is part of a series of investigations into the prevalence of PR in various patient groups and healthy, normally aging adults. Here, we describe a study into the prevalence of PR in a large number of normal healthy subjects, with ages ranging from 17 to 83 years. Our first aim was to find out to what extent PR occur in non-diseased individuals and whether the prevalence of PR increases with normal aging. Furthermore, much more emphasis than has hitherto been the case was put on the importance of screening for health-related factors. Also, we used a well defined battery of PR, following standardized methods of elicitation and scoring.[34] Finally, the study was devised so to make these prevalence data applicable as a reference for other clinical studies in the future.

Extensive cognitive testing was part of the procedure. We will, however, go into this only briefly, as the result of the cognitive part has been published elswehere.[30-32] Another part of the study that is not discussed here, concerns the so-called 'rare' reflexes. These are a group of heterogeneous, infrequent reflexes for which we have not yet gathered enough data to reliably analyze their prevalence. They will be discussed in future publications.

4.3 Methods

4.3.1 Subjects

Subjects were normal, healthy and community-dwelling individuals. They all underwent the rigorous screening for BLE and other health factors described elsewhere.[30,31] Prior to the actual examination, the subjects were screened for evidence of brain damage. Nine subjects did not pass this screening: 6 subjects were mildly demented, as assessed by the Mini Mental State Examination (MMSE)[35], with a score of less than 24, two subjects appeared to have had a major head injury resulting in persisting cognitive dysfunctions. One subject had been treated for brain tumor, which he had forgotten to mention at the pre-screening. If doubt existed about the accuracy of the subject's recollection of the events, their medical files were consulted. Also, it was often possible to gather data provided by relatives to confirm the subject's statements. Thus, we had a large group of selected subjects (n=247) without any a priori likelihood of brain dysfunction or cognitive dysfunctions attributable to a major neurological or psychiatric illness. For the age groups of 70 and 80 years, the number of BLE-affected volunteers exceeded our testing capacity, so that an initial interview over the telephone about BLE had to take place prior to the testing. About another fifty volunteers were excluded at this stage.

Care was taken to balance the level of education in each age group. For this purpose, we used a Dutch scoring system originally developed by Verhage[36]: a 7-point scale, ranging from unfinished primary education (1) to master's degree (7). All subjects were paid for their participation in the experiment.

Table 4.1. Distribution of age within the age groups

	young	middle-aged	old
BLE absent (N=150)			
N	64	40	46
RANGE	17-43	47-64	67-81
M	30.2	54.9	73.3
SD	8.4	5.6	4.3
BLE present (N=97)			
N	30	30	37
RANGE	17-43	47-63	67-83
M	30.9	54.7	74.8
SD	8.6	5.0	5.3

4.3.2 Reflexes

A battery of 14 primitive reflexes (BPR), including a protocol on the application (i.e. how to elicit and score the reflexes), was used[34]. This protocol was shown to have a good inter- and intraobserver reliability[28].

The following reflexes were tested: the glabellar tap, head retraction, palmo- and pollicomental, snout, palmar and plantar grasp, rooting, suck, asymmetrical tonic neck, mouth open finger spread, nuchocephalic, palmar and plantar support reflexes. The PR were divided into three subgroups, following and extending the proposals made by Franssen et al.[10]: the 'nociceptive', the 'prehensile', and the remaining 'other' PR (see table 4.2 for list of PR, subgroups and abbreviations). The signs in the first two groups and the nuchocephalic reflex are well known in research on PR and aging[15]. The remaining four reflexes are known in the realm of child neurology and may be of potential interest in adults[24,25,37].

Table 4.2. Primitive reflexes studied - Subgroups and abbreviations.

Nociceptive reflexes	
1. Glabellar tap reflex	Glab
2. Head retraction reflex	HeRe
3. Palmomental reflex	Palm
4. Pollicomental reflex	Poll
5. Snout reflex	Snout
Prehensile reflexes	
6. Grasp reflex, palmar	GrPa
7. Grasp reflex, plantar	GrPl
8. Rooting reflex	Root
9. Suck reflex	Suck
Remaining reflexes	
10. Asymmetric tonic neck reflex	ATNR
11. Mouth open finger spread reflex	MOFS
12. Nuchocephalic reflex	Nuch
13. Support reflex, palmar	SuPa
14. Support reflex, plantar	SuPl

The general procedure in the BPR protocol was as follows: A basic position as well as instructions to the subject as to what was expected of him/her (e.g., sitting or standing; eyes open or closed, etcetera) were described. No information was given to the subject as to the nature of the expected response. The subject was informed about the nature of the stimulus in order to prevent possible startle reactions, which might influence the required response. Every reflex was measured at least three times, with about two seconds pause between every elicitation, except for the glabellar tap reflex, which was applied two times per second. All reflexes were judged on both the criterion amplitude and on the criterion persistence, in agreement with proposals by others[21-23]. If appropriate, the reflexes were elicited on both sides.

A semiquantified scoring for amplitude as well as persistence of the reflex was applied. A three-point scale for both characteristics was used. The scoring was as follows: For amplitude 0 = an absent response, 1= a weak-moderate response, and 2= a strong response. A description for the weak-moderate and strong amplitudes was given for each reflex separately in the BPR protocol. For persistence 0= absent, 1= response for 1-4 consecutive times, and 2= response for 4 or more consecutive times. The glabellar tap reflex was considered to be present but exhaustible after 4-10, and to be persistent after more than 10 consecutive responses respectively. This is in accordance with the procedure described by others.[9,38] Each reflex was scored in a two-digit code. A detailed description of the entire protocol is described elsewhere.[34]

4.3.3 Statistics

Although data were gathered from seven discontinuous age groups (see table 4.2), for the sake of clarity in graphs and tables, these age groups were clustered into three groups: young (20-40 years), middle-aged (50-60 years), and old (70-80 years). To test for the effects of age, BLE, and gender and possible interactions, ANOVAs were used, with the number of nociceptive reflexes and that of PR as parametric dependent variables. T-tests were used to compare group means of number of PR in various categories. Chi-square tests served to test the occurrence of single reflexes in groups of subjects. Alpha levels of five percent or smaller were taken to denote statistical significance. For the statistical analysis of the number of PR per individual, those reflexes that are elicited bilaterally were regarded to be independent enough to be scored as separate reflexes. The reflex that was observed most frequently (MOFS) was scored bilaterally in only 39% of those individuals who showed the reflex.

4.4 Results

The number of PR in the various groups is given in table 4.3. Figure 1 depicts the percentage of subjects showing any primitive and, more specifically, any nociceptive reflex per age group. Of the prehensile reflexes, the palmar and plantar grasp reflexes and the rooting reflex were never observed. The same was true for the palmar and plantar support reflexes and the asymmetric tonic neck reflex.

Aging. In the total sample of 247 subjects, moderate correlations were found between age and the total of PR (see table 4.3). It appeared that almost one quarter of the young adults showed at least one PR, almost 40% of the middle–aged, and over 80% of the old subjects. The mean number of PR per subject ranges from 0.4 for the young subjects to 1.7 for the old. The average number of nociceptive reflexes increased with age: $F(2,235)=16.00$, $p<.001$, and so did the total number of PR: $F(2,235)=24.79$, $p<.001$. Separate PR were positively related to age, e.g., Snout: $chi^2=42.70$, $p<.001$, and likewise were all other PR that were observed at all, with the exception of the nuchocephalic reflex. This suggests that older people are more likely to show almost any of the reflexes studied here.

BLE. The mean number of PR tended to be somewhat higher in subjects who had experienced BLE, than in those without BLE. However, only for the total of PR the difference due to BLE was significant ($t= -2.09$, $df=245$ (pooled variances), $p<.05$. ANOVA revealed no effect of BLE as to the number of nociceptive reflexes: $F(1,235)=1.00$, n.s., nor as to the total number of PR: $F(1,235)=3.00$, n.s., proving that the group difference (found by t-test) due to BLE is not very robust. Some interesting results were obtained from Chi-square analyses of single BLE: in all 247 subjects, the following BLE were associated with the elicitation of at least one primitive reflex: anesthesia ($chi^2=6.17$, $df=1$, $p<.05$), medication ($chi^2=5.08$, $p<.05$), regular use of benzodiazepines ($chi^2=5.55$, $p<.05$), and mild closed head injuries ($chi^2=5.56$, $p<.04$). Similar results were found when analyzing the occurrence of at least one nociceptive reflex, with the exception of anesthesia. If anything, these results indicate that subjects affected by these BLE are more likely to show primitive reflexes. The suck reflex was the only prehensile sign ever observed in the whole sample: 10 out of 247 subjects. It was, however, significantly associated with BLE: $chi^2=4.13$, $p<.05$). The nuchocephalic reflex and MOFS were not associated with BLE.

Gender. There was no difference in the total of PR between the sexes. In the middle-aged women, an average of nearly twice as many PR could be elicited as in men (0.91 vs. 0.56), although this was not supported by t-test. It did not exist as to nociceptive reflexes, and was not replicated in the other age groups.

Table 4.3. Prevalence of primitive reflexes in normal adults

	All subjects			BLE absent			BLE present		
	young	mid.aged	old	young	mid.aged	old	young	mid.aged	old
# of subjects	94	70	83	64	40	46	30	30	37
Glab	3	4	10	2	1	6	1	3	4
Here	0	0	4	0	0	3	0	0	1
Palm-L	4	3	11	2	1	8	2	2	3
Palm-R	4	4	7	2	2	4	2	2	3
Poll-L	2	1	9	1	0	5	1	1	4
Poll-R	2	1	8	1	0	5	1	1	3
Snout	7	12	40	5	5	20	2	7	20
Any nocic. R.	13	18	49	8	7	27	5	11	22
Mean # of nocic. R.	0.2	0.4	1.1	0.2	0.2	1.1	0.3	0.5	1.0
Max. # of nocic. R.	5	4	6	5	3	6	4	4	5
Suck (prehens.)	0	0	10	0	0	3	0	0	7
Nuch-L	0	5	6	0	3	3	0	2	3
Nuch-R	1	4	0	0	2	0	1	2	0
MOFS-L	8	10	21	7	5	9	1	5	12
MOFS-R	5	7	14	4	5	4	1	2	10
Any prim. R.	21	30	64	15	15	34	6	15	30
Mean # of prim. R.	0.4	0.7	1.7	0.4	0.6	1.5	0.4	0.9	2.0
Max. # of prim. R.	6	5	9	6	3	6	4	5	9

Note. Of the prehensile reflexes, the palmar and plantar grasp reflexes and the rooting reflex were found in none of the subjects.

ANOVA revealed no interaction with age, but did so with BLE ($F(1,225)=6.882$, $p<.05$), indicating that BLE-affected women show more PR as an effect of BLE than men. None of the separate PR proved to be associated with gender.

Scoring. The amplitude of virtually all reflexes, if present, was scored as weak to moderate (score '1'). Only three MOFS (one in the BLE group) and two pollicomental reflexes (both in the BLE group) showed a strong response. Persistence of reflexes was found more often in the middle–aged and old subjects than in the young, especially with the MOFS and snout reflexes. Of all BLE–free subjects 23% showed a MOFS, of which 39% was persistent and 20% had a snout reflex of which 30% persisted. For the subjects with BLE the

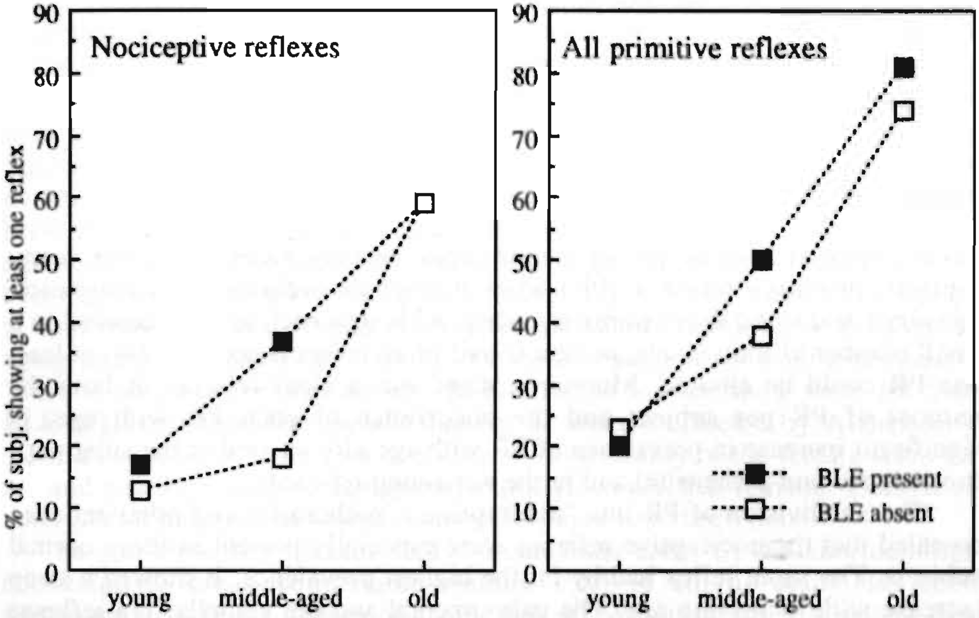

Figure 4.1. Left: % of subjects showing any nociceptive reflex (Glab, Here, Palm, Poll, Snout). Right: % of subjects showing any primitive reflex (GrPa, GrPl, Root, Suck, ATNR, MOFS, Nuch, SuPa, SuPl and nociceptive reflexes).

scores are for MOFS: 33% with 71% persistence, and snout: 30% with 55% persistence. To a lesser extent the palmo– and pollicomental reflexes also showed more persistence in the BLE-group. The suck reflex persisted four times in the BLE group and once in the group without BLE.

Left/right differences. There was a tendency for those PR that were elicited on both sides of the body to prevail on the left side, however this difference was only significant as to the MOFS (sign test, $Z=2.23$, $p<.05$).

Other personal variables. Number of PR and occurrence of separate PR were not related to other background variables such as educational level, involvement in social activities, hobbies or sports.

Cognitive functions. Of all cognitive functions studied in this group, a compound score for memory function was devised, encompassing delayed recall and recognition of newly learned verbal material.[32] Although memory appeared to be associated with the existence of any of all PR studied (not with nociceptive reflexes only): $chi^2=17.15$, $df=8$, $p<.05$, this association could largely be explained by aging, as within each age group there was no association at all. The same was true for the separate reflexes, none of which was observed to be associated with cognition. This can be taken to denote that the higher prevalence of PR and cognitive decline are independent and both age-associated. In a similar vein correction for BLE eliminated any association of cognition with PR.

4.5 Discussion

In 247 normal healthy subjects with ages varying from 20 to 80 years, fourteen primitive reflexes (PR) were studied to evaluate their diagnostic relevance and to establish normative data. Although each reflex occurred in a small number of individuals, in almost half of all subjects tested (47%) at least one PR could be elicited. Moreover, there was a clear relation of both the number of PR per subject and the occurrence of each PR with age. A significant increase in prevalence of PR with age also existed in the subgroups (nociceptive and prehensile) and in the remaining reflexes.

The subdivision of PR into 'nociceptive', 'prehensile' and other reflexes revealed that the nociceptive reflexes were especially present in these normal subjects. The snout reflex had by far the highest prevalence. It showed a steep increase with increasing age. The palmomental and the glabellar tap reflexes had moderate prevalences. Prehensile reflexes were virtually not observed, with the exception of the suck reflex, which appeared only in the very aged. The nuchocephalic reflex was present in the middle–aged even somewhat more often than in the old subjects, which casts doubt as to its specificity as a sign of diffuse cerebral dysfunction.[1] The MOFS was present more often in the young BLE–free subjects and in the old subjects with BLE. In child neurology, the presence of the MOFS is considered to be a sign of retardation of nervous functioning.[37] In the young subjects in our series no sign or symptom of retardation was present in their medical history or during examination. The higher prevalence of the MOFS in the old category, especially in the subjects with BLE, may perhaps be considered as a sign of disinhibition, without any clear underlying pathology.

As to PR and age, our findings are in accordance with the results of Jacobs and Gossman.[12] They examined (only) three reflexes in 105 healthy volunteers in the third through ninth decade of life. They found the palmomental reflex and the snout to be the most common; the latter, in their series too, was the most age sensitive. The methodology was described; the subjects appearantly were in good health, however no screenig for BLE was carried out. Other studies, as those mentioned in the introduction, have different drawbacks: the number of PR studied is usually limited, and the methodology lacks a scrupulous description.[4–8,17,33] The populations are often small, and mainly elderly people are studied.[16,19] Studies in retirement facilities often yield mixed samples of subjects, and the screening for health may be insufficient.[17,33]

In many instances an association of PR with health-related factors (BLE) could be established, although the findings obtained with PR are less conclusive than the role of health screening and BLE in connection with cognitive functioning. Nevertheless, there was an overall tendency of BLE to affect the number of PR. Also, some BLE (anesthesia, medication, benzodiazepines and brain trauma) were clearly associated to the prevalence of PR. This underlines again the great importance of a very thorough and rigorous screening for every age-extrinsic health-related factor. Once again, Rowe's and Kahn's point is confirmed that one should control for all factors that are not inherent to aging as such, in order not to study disease dysfunctions or even processes.[29] There is no clear explanation why BLE–affected women show more PR than BLE–affected men. The greater number of women affected by Alzheimer's disease could be an indication of a greater vulnerability of the female brain for in– and possibly extrinsic damaging factors. However, this remains speculative until greater numbers of observations in this area have been done.

In our view, the present study circumvents some of the shortcomings connected to other, comparable studies. First of all, no study has been performed on a broad battery of 14 PR before, permitting the assessment of a primitive reflex profile. Secondly, though some studies have described the methods of elicitation and scoring, there is no protocol on the examination of PR that contains instructions to the examiner and the patient and that uses a semiquantified, separate scoring for both amplitude and persistence. Thirdly, with the exception of the study of Jacobs and Gossman,[12] no other normative study on PR in a large number of healthy adults of all age groups has been performed. Finally, no other study has till now taken into account the presence or absence of BLE in the selection of their subjects. As the findings in these subjects may have served as normative data for controls in other clinical studies, this seems an important fact to keep in mind in the review of reports from the past. Therefore it is necessary that, when normative data about PR are gathered in adult volunteers, they should be thoroughly screened on BLE.

PR are traditionally considered as the consequence of physiological aging. However, by some authors, PR are thought to represent dysfunctions of the central nervous system. In this study it has become clear that many of the PR may occur at any age in thoroughly screened, healthy adults. The clear increase of PR with increasing age cannot, at least for the nociceptive signs, be ascribed to disease, based on these findings. Further investigation is needed to replicate and establish the role of BLE observed here. In the mean time, the possible influence of BLE in the medical history on the prevalence of PR should not be denied.

Studies on PR in well–defined patient groups will have to be carried out in order to investigate the claims that (some) PR are pathognomonic or localizing signs. The use of a standardized protocol for the examination of PR and of reliable data on the prevalence of PR in normal, healthy control subjects who are thoroughly screened on BLE, are indispensable in this. As was stated by Calne et al.,[38] "The dilemma of defining control populations is of more than philosophical importance".

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5 Primitive reflexes in age-associated memory impairment

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5.1 Summary

The prevalence of eight primitive reflexes (PR) was examined in 15 patients with age-associated memory impairment (AAMI) following a standardized protocol and compared with two matched control groups either unaffected or affected by age-extrinsic health-related factors: 'biological life events' (BLE). The total number of PR and the number of nociceptive PR were significantly higher in the patient group and in the control group with BLE than in the control group without BLE; if PR were detected in these groups they showed considerably more persistence (lack of habituation) than in the control group without BLE. It was concluded that AAMI patients may represent a -possibly heterogeneous- group of subjects who may have suffered from certain BLE, as reflected by memory complaints and by a high prevalence of some PR. Assessment of the presence of PR may be helpful in the differential diagnosis in patients with cognitive problems. Furthermore, control subjects should be thoroughly screened for BLE in their medical history.

5.2 Introduction

Adult neurological patients may exhibit a number of reflexes that are also present in the earliest stages of ontogenetic development. These developmental, or primitive, reflexes (PR), also referred to as 'release signs', are normally present in fetal life, in the newborn or infant and gradually disappear with increasing age. Through the years, there have been claims that various PR are pathognomonic signs for or strongly associated with neurological conditions such as Parkinson's disease[1,2] or dementia.[3–7] However, the clinical value of PR has not been established and several authors question the value of PR in a routine clinical neurological investigation.[8–10] This is because PR can also be elicited in healthy elderly subjects.[11–13] Already in 1949, Howell[14] found aberrant neurological signs to be common in a group of 200 supposedly healthy male pensioners and warned against making misdiagnoses in the elderly. Hildenhagen and Schiffer[15] made similar findings. Vreeling et al.[16]

found an increasing prevalence of certain PR with age in a recent study of 247 healthy adults. Thus some authors feel that PR have no specific diagnostic value but are merely a sign of the physiological aging process.[8,17]

De Ajuriaguerra and Hécaen[18] hypothesized that PR in mature subjects represent release phenomena, caused by a decrease in higher cortical control over lower centers. According to this hypothesis, reflexes that exist in earlier stages of ontogenesis are suppressed as the brain matures, to reappear with diminution of cerebral inhibition: "once a man, twice a child". Delwaide and Dijeux[19] found evidence in their longitudinal study of Alzheimer patients that primitive reflexes reappeared in the reverse order in which they develop in childhood. This 'retrogenesis' was predicted by De Ajuriaguerra and Hécaen, following Hughlings Jackson's postulate that in the evolution of the central nervous system, a hierarchic development from lowest to highest cerebral centers takes place and that in nervous disease the reverse may take place, 'dissolution' to a lower level.[20]

It remains to be established, however, whether PR that are elicited in presumably healthy elderly persons are the consequence of the physiological aging process itself or that subtle health-related factors also contribute to the (re)appearence of these signs. For instance, Houx et al. showed that people who were regarded as healthy according to criteria used in gerontological research, could be differentiated into two subgroups: those who were or were not characterized by the presence of 'Biological Life Events' (BLE).[21] These BLE are factors that have relatively little influence on the brain, such as a very mild brain trauma or (surgery under) general anesthesia, and other conditions (see table 5.1). Subjects with BLE had inferior performance on neurocognitive tests taken as a measure of brain function; this was especially the case in subjects older than 60 years. Elderly subjects with BLE also showed more PR than their thoroughly screened age-compeers without BLE.[16] This leaves us the question of what constitutes 'normal aging'. In the light of these findings it is questionable whether studies that investigate the presence of PR in normal elderly subjects (versus elderly neur-ological patients) have really found evidence for the presence of PR in healthy elderly subjects. It may very well be that these groups of 'healthy' elderly subjects are heavily compromised by the presence of non-diseased, but sub-normal individuals in whom the presence of PR and other soft neurological signs might be ascribed to BLE. Thus, the presence of PR would indeed signify subtle changes in the brain. Findings showing a correlation between the presence of PR and decreased cognitive functioning are consistent with this.[22-24]

Recently, Franssen et al.[25] noted that the neurological changes that occur in the earlier stages of dementia may not always be evident on routine testing, but that the problem might to some extent be addressed by rating the observed clinical signs on a scale, and by looking for patterns in groups of individual

Table 5.1. Factors associated with brain dysfunctions and/or cognitive decline: Biological Life Events (BLE; adapted from Houx et al.).[19]

1. Present or past treatment by a neurologist for TIA, epilepsy, migraine, meningitis, encephalitis, brain trauma etc.;
2. Present or past treatment for diseases with possible repercussions on the brain (e.g., renal dysfunction, diabetes mellitus, thyroid dysfunction). Hypertension not included;
3. More than 3 concussions, or 1 with a PTA of more than 1 hour;
4. General anesthesia more than 3 times or 1 time for more than 3 hours;
5. Use of medication that affects driving ability or consciousness;
6. Alcohol abuse (i.e. more then 35 glasses per week for men and 21 for women);
7. Neurotoxic factors, such as exposure to organic solvents or substance abuse;
8. Present (or less than 5 years ago) treatment by a psychiatrist;
9. Complications at birth or developmental problems in early childhood.

signs as the illness progresses. They found significantly higher scores on summed variables that combined the scores for various individual neurological measures. PR were divided into two subgroups: nociceptive and prehensile signs. The latter prevailed in the late stages, the nociceptive PR were more prevalent in the early stages of dementia. This has also been observed in nondemented subjects with mild memory impairment, i.e. stage 3 on the Global Deterioration Scale (GDS).[26] Recent findings showed that healthy elderly subjects with incidental cerebral lesions, as measured by MRI scan, had a higher prevalence of PR.[27]

The present paper is part of a series of investigations into the prevalence of PR in various groups of adult neurological patients and healthy subjects. It is the aim of this paper to investigate whether aged subjects who complain of diminished memory functions, but who are not demented, are characterized by an increased number of PR when compared to two groups of age-matched, healthy control subjects without memory complaints, but with or without BLE in their medical history. In the present study, only patients fulfilling the inclusion and exclusion criteria for AAMI according to Crook et al.[28] were investigated. AAMI is a recently defined state, which describes loss of memory function in otherwise healthy persons aged at least 50 years (see table 5.2 for inclusion and exclusion criteria). It concerns a relatively modest impairment, with adequate intellectual functioning, but is thought to be common enough to

Table 5.2. Inclusion and exclusion criteria for AAMI

1. Inclusion criteria:	
a.	Age above 50 years.
b.1.	Complaints of memory loss reflected in everyday problems.
b.2.	Onset of memory loss gradual, without sudden worsening in recent months.
c.	Memory test performance at least 1 standard deviation below the mean established for young adults in a test of secondary memory with normative data.
d.	Evidence of adequate intellectual function as determined on the Vocabulary subtest of the Wechsler Adult Intelligence Scale.
e.	Absence of dementia as determined by a score of 24 or higher on the Mini-Mental State Examination.
2. Exclusion criteria:	
a.	Evidence of delirium, confusion, or other disturbances of consciousness.
b.	Any neurological disorder that could produce cognitive deterioration.
c.	History of infective or inflammatory brain disease.
d.	Evidence of cerebral vascular pathology as determined by the Hachinski Ischemia Score or by neuroradiological examination.
e.	History of repeated minor head injury or one major head injury.
f.	Current psychiatric diagnosis (according to DSM-III criteria) of depression, mania, or major psychiatric disorder.
g.	Current diagnosis or history of alcoholism or drug dependence.
h.	Evidence of depression as determined by the Hamilton Depression Rating Scale.
i.	Any medical disorder that could produce cognitive deterioration.
j.	Use of any psychotropic substance or any other drug that may significantly affect cognitive function.

Source: Crook et al.[28]

be a feature of normal aging. However, the question arises whether the memory impairment accompanying normal or usual aging is a matter of physiological decline.

There is considerable interest among memory researchers to establish the neuropathological[29] and neurochemical[30] basis of this condition. The rationale for investigating this group of patients is that they may suffer from brain damage caused by age-extrinsic factors, in addition to the physiological aging process, or that they may be in a prodromal phase of a dementing condition. If PR are considered as signs of (diffuse) cerebral dysfunction, it is to be expected that their prevalence is increased in subjects with supposed damage to the brain.

Subjects in this study were in GDS stage 2-3, a phase in which other investigators have also found PR,[25] but no significant decrements in various behavioral, cognitive and neuroradiological measures.[31] PR might thus be of help in differentiating between the first three stages. A second reason for this investigation was that in none of the few studies on this subject a broad PR 'profile' has been studied and compared in AAMI patients. Another motive was to compare the AAMI group with two groups of control subjects, namely with and without BLE, which has not been done earlier to our knowledge.

A battery of eight primitive reflexes (BPR) relevant to the assessment of neuropsychiatric disorders[13] was used. The following reflexes were examined: the palmomental, the snout, the glabellar tap, the grasp, the suck, and the nuchocephalic reflexes. The mouth-open-finger-spread reflex was added because of its possible value in adult neurology.[32] The pollicomental reflex was also added because, according to Bracha,[33] this modification of the palmomental reflex is highly sensitive and specific for damage in the contralateral frontal premotor cortex (see table 5.3 for reflexes, abbreviations and categories).

Table 5.3. Primitive reflexes studied - Abbreviations.

Nociceptive reflexes	
1. Glabellar tap reflex	Glab
2. Palmomental reflex	Palm
3. Pollicomental reflex	Poll
4. Snout reflex	Snout
Prehensile reflexes	
5. Grasp reflex	Grasp
6. Suck reflex	Suck
Remaining reflexes	
7. Mouth open finger spread reflex	MOFS
8. Nuchocephalic reflex	Nuch

The hypotheses tested in the present study were: 1. AAMI patients are characterized by an increased number of PR, when compared with healthy control subjects without BLE, 2. this increase especially concerns the nociceptive signs, and 3. no significant difference in PR will be found between the AAMI patients and the control group with BLE.

5.3 Subjects and methods

Subjects. We studied 15 community-dwelling AAMI patients (5 male / 10 female) enrolled at the Maastricht Memory Clinic, a specialized health care facility which is part of the Departments of Psychiatry and Neurology of the University Hospital in Maastricht, The Netherlands. The patients had been referred by general practitioners, psychiatrists, and neurologists because of problems in cognitive functioning, most often problems concerning memory and concentration. None of the patients received medication. Control subjects were drawn from a large population of subjects who had responded to an advertisement in a local newspaper. (See table 5.4 for characteristics). These control subjects were normal and healthy and had no health complaints; one group (control I) of 15 subjects had and the other group (controls II) had not experienced BLE. They were matched to individual patients in the AAMI group in terms of age, sex and level of education. The groups of patients and control subjects thus consisted of matched trios.

Table 5.4. Characteristics of patients and control subjects.

	Patients (N=15)		Controls I (N=15)		Controls II (N=15)	
Age (mean)	67.7	(6.2)	67.1	(6.1)	66.3	(6.3)
Age (range)	55 - 75		57 - 77		53 - 77	
Sex	5 M / 10 F		5 M / 10 F		5 M / 10 F	
Education	4.8	(1.3)	4.6	(1.3)	4.3	(1.2)
G.D.S.	2.5	(0.5)	–		–	
B.D.S.	1.3	(1.5)	–		–	
M.M.S.E. (mean)	28.4	(1.5)	–		–	
M.M.S.E. (range)	24 - 30		–		–	
H.I.S.	2.0	(0.7)	–		–	
H.D.S.	7.3	(3.2)	–		–	

Note: See text for abbreviations. The numbers between brackets denote standard deviations.

All patients in the memory clinic underwent a thorough clinical evaluation, consisting of a neurological and psychiatric examination as well as an extensive battery of neuropsychological tests as described by Verhey et al.[34] Routine laboratory investigations and CT scan of the brain were carried out. This information was used by a multidisciplinary medical team to assign a diagnosis to each subject. Various rating scales were used, namely, the Hamilton Depression Rating Scale (HDRS),[35] Global Deterioration Scale (GDS),[26] Blessed Dementia Scale (BDS),[36] Hachinski Ischemic Score (HIS),[37] and the Mini Mental State Examination (MMSE).[38]

The assignment to the AAMI group was based upon the diagnostic criteria proposed by Crook and coworkers.[27] Information regarding subjective memory complaints and their onset was obtained in interviews with a 'significant other'. Intellectual function was assessed with the Dutch version[39] of the Wechsler Adult Intelligence Scale,[40] or with the Dutch Groningen Intelligence Scale.[41] Patients with an overall (verbal) IQ score of 97 or more were included. This is in line with Crook's proposal that patients with a score on the Vocabulary subtest of > 32, which is equivalent to an estimated total IQ of 97 or more, be included.[42] The control subjects underwent a routine physical and neurological examination and a neuropsychological investigation. None of the control subjects had signs or symptoms of mood disturbances or cognitive decline. They were paid for their participation.

Procedure. The general procedure in the BPR protocol was as follows: A basic position was described (e.g., sitting or standing; eyes open or closed, etcetera). No information was given to the subject as to the nature of the expected response but the subject was always informed about the nature of the stimulus in order to prevent possible startle reactions, which might influence the response. Every reflex was measured at least three times, with about a two second pause between every elicitation, except for the glabellar tap and the nasopalpebral reflexes, which were applied two times per second. All reflexes were judged on the criterion amplitude and on the criterion persistence, in agreement with others.[43] If appropiate, the reflexes were elicited on both sides.

Amplitude and persistence of the reflex were scored semiquantitatively. A three-point scale for both characteristics was used. The scoring was as follows: For amplitude 0= an absent response, 1= a weak-moderate response, and 2= a strong response. The weak-moderate and strong amplitudes were described separately for each reflex in the BPR. For persistence 0= absent, 1= response for 1-4 consecutive times, and 2= response for 4 or more consecutive times. In accordance with Sunohara et al.,[44] the glabellar tap and the nasopalpebral reflexes were considered to be present but exhaustible after 4-10, and to be persistent after more than 10 consecutive responses, respectively. A detailed description of the entire protocol is available on request to the first author.[45]

5.4 Results

The prevalence of PR and their persistence is shown in the figure. Of all PR, 28% were found positive in the patient group, 14% in the first control group (with BLE), and less then 4% in the second control group (without BLE).

The differences between the groups for the individual reflexes were particularly pronounced for the pollico– and palmomental reflexes. The pollicomental reflex was found positive in almost three quarters of the patients (86 and 57% on the left and right side, respectively). The palmomental reflex was present in over half of the patients (60% and 53%), whereas only 6.7% of the control subjects with BLE, and none of the control subjects without BLE showed these reflexes. The snout reflex was present in 40% of the patients, but it was also found in 60% of the subjects with BLE, and in 20% of the subjects without BLE. The glabellar blink and the suck reflexes did not occur in the patients and they were scarce in the subjects of both control groups; MOFS and nuchocephalic reflexes were somewhat more frequent and persistent in the control subjects with BLE. The grasp reflex was not present in any of the subjects. Most reflexes were found slightly more often on the left side of the body than on the right side. There was virtually no difference between the sexes as far as the prevalence of PR was concerned.

None of the findings for amplitude in the patients or in the control subjects was scored as a '2', which means that no reflex was judged as being very brisk. However, the scores for persistence, as shown in the bars in the figure, were quite different in the three groups. In the patients more than half of the positive palmomental reflexes were persistent, and more than three quarters of the pollicomental reflexes. Two of the six positive snout reflexes persisted. In the control subjects with BLE persistence was found in about half of the positive snout, suck, MOFS, and nuchocephalic reflexes. In the control subjects without BLE none of the (few) positive reflexes were persistent.

In addition to the eight individual reflexes, two summary measures were made, consisting of combinations of several reflexes as described above.[25] Thus, the snout, glabellar tap, palmomental, and pollicomental reflexes were combined into a subgroup called 'nociceptive' reflexes. The sucking and grasping reflexes were combined into the 'prehensile' reflexes. The rooting reflex, also considered a prehensile sign, was not recorded in this study. The MOFS and the nuchocephalic reflexes formed a rest group.

In the AAMI group the BDS score correlated with the total number of PR, and with the number of nociceptive and rest–group reflexes: Spearman rank order correlation between 0.64 and 0.51, $p<.05$. In the control groups no correlation was found between age, education, and number of reflexes, total or in subgroups.

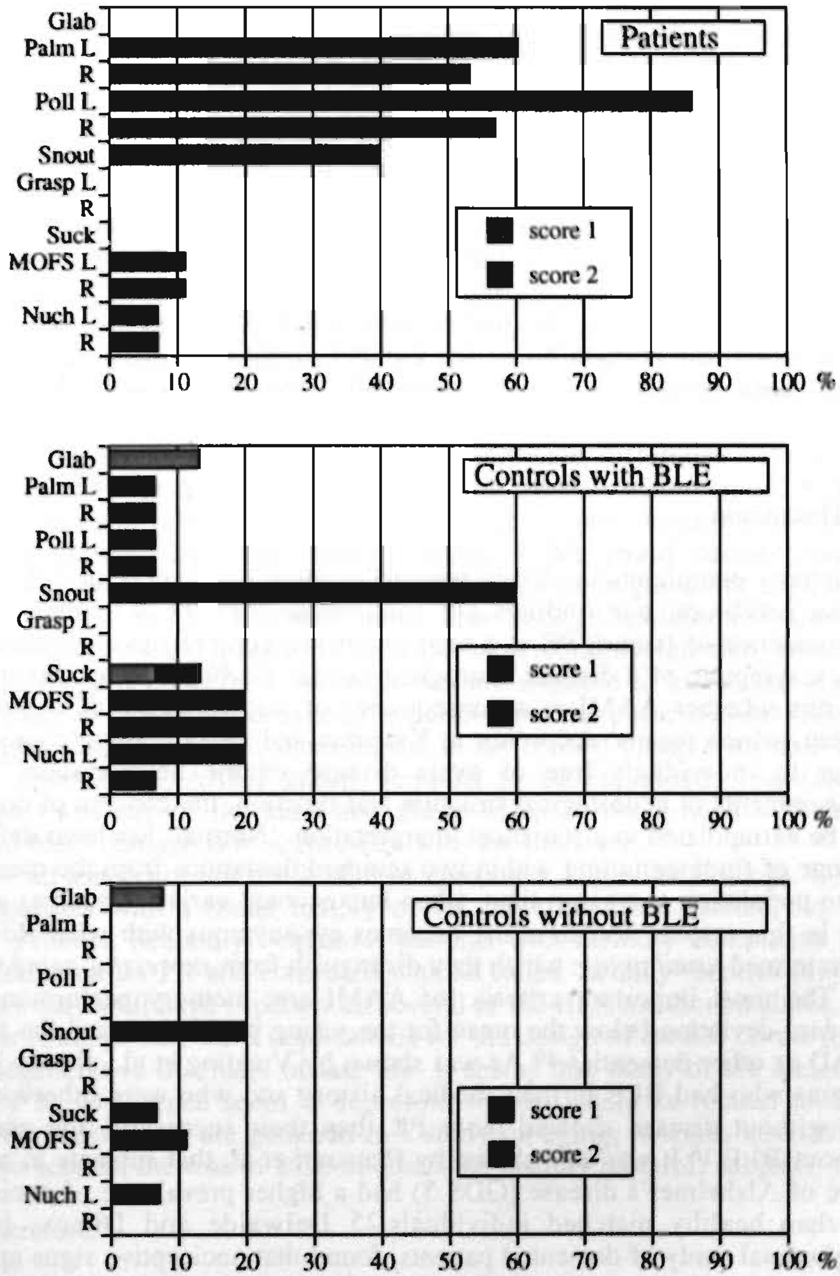

Figure 5.1. Percentage of subjects showing a PR, either persistent (score 2) or non-persistent (score 1), in the three groups (see table 5.4).

No significant difference was found between the AAMI patients and the control subjects with BLE in the numbers of all PR, the nociceptive, and the rest–subgroup of reflexes. The number of prehensile signs was too low for testing. There were more PR and nociceptive reflexes in the AAMI patients than in the control subjects without BLE ($t = -2.866$, $df=28$, $p<.01$ and $t = -3.125$, $p<.01$ resp.). The difference in the rest-subgroup was not significant, and again the number of prehensile signs was insufficient for testing. The total numbers of PR as well as the number of nociceptive signs were higher in the group with BLE than in the BLE-unaffected group ($t = -3.307$, $p<.01$ and $t=2.323$, $p<.05$ resp.). The higher prevalence of the rest-group reflexes (MOFS and nuchocephalic) in the control group with BLE did not reach significance ($p=0.072$), and the prehensile signs hardly occurred in either control group.

5.5 Discussion

If memory complaints in elderly persons in some way represent dysfunctions of the cerebrum, our findings are compatible with the statement that the reappearence of (some) PR is a sign of diffuse cerebral involvement, rather than a symptom of a distinct neurogical disease.[3,4,46] However, the question remains whether AAMI is a consequence of normal aging of the nervous system, which means, according to Katzman and Terry, "aging changes that occur in individuals free of overt disease of the neurosystem".[47] For measurements of neurological structure and function, the concept of normality can be extrapolated to a statistical interpretation. 'Normal' has been defined as a range of findings falling within two standard deviations from the mean for a given population at a given time, taken into account variables such as age and sex. In this respect normal aging becomes synonymous with what Rowe and Kahn termed *usual aging*, which they distinguish from *successful aging*.[48]

The most important criteria for AAMI are: memory performance one standard deviation below the mean for the young population, and the absence of AD or other dementias.[49] As was shown by Vreeling et al., elderly healthy persons who had BLE in their medical history and who were otherwise well and without disease showed more PR than their successful age compeers without BLE.[16] It was also shown by Franssen et al. that subjects in an early stage of Alzheimer's disease (GDS 3) had a higher prevalence of nociceptive PR than healthy matched individuals.[25] Delwaide and Dijeux, in their longitudinal study of demented patients, found that nociceptive signs appeared first, their prevalence decreasing as the dementia progressed, while the number of prehensile reflexes increased.[19] This is in line with the 'retrogenesis' theory of de Ajuriaguerra and Hécaen[18] based on Jacksonian principles. Kobayashi et al. found three nociceptive reflexes (glabellar, snout, and palmomental) to be significantly more prevalent in otherwise healthy subjects with incidental lesions (on MRI) of the brain compared with subjects without these lesions; regional cerebral blood flow, brain atrophy and intellectual ability did not differ in the two groups.[27]

In the present study there were considerably more PR in AAMI patients, than in healthy, BLE–free control subjects. This is especially true for the nociceptive signs such as the palmomental, the pollicomental and -to a lesser extent- the snout reflexes. Not only the number, but also the persistence of these PR was significantly higher in the patients than in the BLE–free control group. In this respect, AAMI and the PR that accompany it can be considered to be a consequence of damage to the brain of -up to now- unknown nature; in other words, damage possibly caused by some form of BLE. This statement is supported by the fact that there was no significant difference between the prevalence of PR in AAMI patients and control subjects with (certain) BLE.

No particular reflex was pathognomonic for organic brain dysfuntion, as has been claimed by some researchers.[13,33] We could neither confirm Bracha's claim that the pollicomental reflex is a pathognomonic sign of an organic lesion in the premotor area, nor Jenkyn's statement that the nuchocephalic reflex is a sensitive indicator of cerebral dysfunction, at least as far as memory is concerned. More studies are required to assess the clinical equivalence or difference between the palmo- and the pollicomental reflexes. The high prevalence of the snout reflex, in the control group with BLE even higher than in the AAMI group, remains to be explained. The (almost complete) absence of the suck and grasp reflex in the groups with no or minimal brain damage is in accordance with the literature.

Not all aspects of our results can be compared with other findings. Firstly, investigations with a broad battery of PR have not been carried out with AAMI patients. Secondly, whenever patients with memory complaints have been examined for PR and compared with so called 'healthy' control subjects, the latter may well have experienced several of the BLE mentioned above.

Our findings may have implications for the design of studies on the major neurodegenerative disorders of late life. It seems that many of the undefined changes in senescence seem to represent minimal deficits related to BLE. When normative data are gathered in a study on aging, it seems advisable to take into account the role of BLE in otherwise healthy (control) subjects.

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6 Primitive reflexes in Alzheimer's disease and vascular dementia

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6.1 Abstract

Data on the prevalence and clinical value of primitive reflexes (PR) in dementia are controversial. This is mainly due to a lack of standardization of the methods by which these signs are elicited and scored. A standardized protocol was used to investigate eight PR in 20 patients with Alzheimer's disease (AD), 20 patients with vascular dementia (VD), and 20 control subjects for each group. Both patient groups showed considerably more PR than the control groups. The prevalence of PR was related to the severity of dementia. No single reflex or combination of PR pathognomonic for dementia could be distinguished. The 'PR profiles' of AD and VD patients were similar.

6.2 Introduction

Demented patients may exhibit a number of reflexes that are also present in the earliest stages of ontogenetic development. These developmental or primitive reflexes (PR), also referred to as 'release signs', are generally present in fetal life, in the newborn or infant and gradually disappear with increasing age. They may re-appear in senescence and with neurological disease.

Over the years, there have been claims that various PR are strongly correlated with dementing conditions such as Alzheimer's disease (AD),[1–5] vascular dementia (VD),[2,6-9] or dementia in Parkinson's disease.[10,11] In addition, several authors have argued that (particular) PR may be of clinical value as indicators of cognitive dysfunction,[4,5,12,13] or impaired ADL function and dysfunctional behavior.[14] Diffuse hemispherical damage,[1,15,16] and focal lesions, notably of frontal areas, have also been mentioned in this respect.[17–19] Some authors[19,20] have found a correlation between the prevalence of PR and cortical atrophy whereas others have not.[21] Recently, PR were investigated in community-dwelling AD patients versus non demented controls.[5] Although PR occurred with increased prevalence in the patients, they occurred too infrequently early in the course of AD to serve as diagnostic markers. In another study, release signs occurred in 55% of patients with AD, but they were also present in 9% of control subjects[22]; patients in a late stage of AD did not show a significantly increased prevalence of PR compared with subjects in the early stage of AD. The conclusion was that these signs were neither sufficiently sensitive, nor sufficiently specific to serve as a diagnostic marker for AD. Similar findings and conclusions were drawn in two other studies.[23,24] However, it was recently found that when compound scores were made for various subgroups of reflexes, patients in a late stage of AD had a significantly increased prevalence of grasp, root and suck reflexes (the *prehensile* signs) compared with control subjects and patients in an early stage of AD, who showed more glabellar, snout and palmomental reflexes (the *nociceptive* signs).[4] Others question the clinical value of PR in a routine neurological examination and they consider the (re–)appearance of PR merely as a sign of physiological aging, being of no clinical use in the examination of demented persons.[25–27]

The potential contribution of PR to the differential diagnosis of dementing conditions is unclear. This is because PR are also prevalent among normal elderly people,[28–30] in other neurological diseases, such as Parkinson's disease,[31,32] in psychiatric disorders[33] and in non-demented patients with vascular abnormalities of the brain.[7,34] PR have been reported to predominate in VD with lacunae, especially in the frontal lobes,[6] and in leuco-araiosis.[7] The clinical value of PR in distinguishing AD from VD could not be established by Marterer et al.[13] They found no significant difference in prevalence of the glabellar tap and the grasp reflexes in patients with AD and multi-infarct dementia (MID). However, straightforward studies in which a "primitive reflex profile" (PRP) of AD and VD patients have been compared, have up till now not been performed.

Thus, the literature on PR in dementing conditions is often controversial. This seems to be due, in the first place, to heterogenity of the patient groups studied. Secondly, there is a lack of compatibility between the methods used to elicit and score PR. Thirdly, the number of PR studied was usually small, rarely exceeding three reflexes, so that a reflex profile could not be established. Fourthly the PR that were examined were often mutually exclusive. These factors may have led to incompatibility between the various studies and (thus) to different findings and conclusions about the clinical relevance of PR in dementia.

The present paper investigates the prevalence of eight PR in a group of community-dwelling AD and VD patients, and healthy control subjects that were carefully matched for age. The aim was to assess the effect of dementia on the prevalence of PR, independent of the effect of aging, as suggested by others.[1,5,28] Because of the suggested relation between the prevalence of PR and the severity of dementia,[4,8,35,36] cognitive functioning and the stage of dementia were also assessed. We decided to investigate community-dwelling patients because many of the earlier studies examined patients in a late stage of dementia. It is difficult to differentiate between AD and VD in the early stages and it is not yet known if PR other than the glabellar or grasp reflexes or a PRP will be useful in distinguishing between these conditions. A clinical 'primitive reflex profile', consisting of 8 PR has not been studied in demented subjects. Recently, in our methodological study on PR in healthy adult volunteers and different categories of neurological patients,[37] we found that experienced neurologists differ considerably in how they elicited and judged PR, even after basic consent on the methods had been obtained. Application of a standardized PR protocol, in which the instructions to the patient and the examiner, and the way of elicitating and scoring of the PR are described in detail, markedly increased inter– and intra-observer reliability.

The first aim of the present study was thus to apply a standardized battery of PR (BPR) to demented patients, to assess the prevalence of these signs in patients with AD or VD compared to healthy controls. The second aim was to determine the clinical value of these reflexes, by correlating them to parameters such as age and sex, severity of the disease, cognitive functioning, and depression. The third aim was to investigate if the PRP could be used to differentiate between AD and VD.

The reflex battery consisted of three categories of PR (see table 6.1). The first category consisted of reflexes often mentioned in relation to brain pathology in adults and/or in a brain aging perspective, namely the glabellar tap,[38-40] palmar grasp,[17,41] palmomental,[3,42,43] snout,[31,44] and suck[16,44] reflexes. The second category consisted of PR that are not often used, but are

Table 6.1. Primitive reflexes studied - Abbreviations.

Nociceptive reflexes	
1. Glabellar tap reflex	Glab
2. Palmomental reflex	Palm
3. Pollicomental reflex	Poll
4. Snout reflex	Snout
Prehensile reflexes	
5. Grasp reflex, palmar	GrPa
6. Suck reflex	Suck
Other primitive reflexes	
7. Mouth open finger spread reflex	MOFS
8. Nuchocephalic reflex	Nuch

mentioned by some authors in relation to brain aging and brain pathology, namely the nuchocephalic[15,45] and pollicomental[3,46] reflexes. The mouth open finger spread reflex (MOFS) is used in child neurology and may have potential value in the use in adults.[47,48]

The order in which the PR are listed in table 6.1 is in accordance with the proposals of Franssen et al. (v.s.).[4] Reflexes no. 1–4 are 'nociceptive' signs, reflexes no. 5 and 6 are 'prehensile' signs (the rooting reflex was not examined in this study), and the remaining reflexes, no. 7 and 8, are categorized as 'other' reflexes. The first group is termed nociceptive because each of them shows a facial contraction to a potentially noxious stimulus. The second category is termed prehensile because they seem to represent part of a prehensile syndrome (as described by de Ajuriaguerra[44]), eventually evolving into paraplegia in flexion, described by Yakovlev.[49]

6.3 Subjects and methods

We studied 40 community-dwelling patients with dementia enrolled at the Maastricht Memory Clinic, a specialized health care facility which is part of the Departments of Psychiatry and Neurology of the University Hospital in Maastricht, The Netherlands. The patients had been referred to this department by general practitioners, psychiatrists and neurologists (see table 2 for characteristics). Twenty patients (12 females, 8 males) with probable Alzheimer's disease (AD) and 20 patients (12 males, 8 females) with vascular dementia (VD) were studied. None of the patients received medication that could affect the ability to drive ('yellow sticker medication'), and/or that could have a possible influence on consciousness.

Probable AD was diagnosed according to the NINCDS-ADRDA guidelines of McKhann et al.[50] AD patients whose Hachinski ischemic score (HIS)[51] was 4 or more were excluded from the study. A HIS score above 7 is essential for a diagnosis of VD. Most VD patients had a history of hypertension and evidence of cerebrovascular disease on CT– scans of the brain. Dementia was diagnosed according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, revised third edition (DSM III–R).[52]

All patients underwent a thorough neurological and psychiatric examination as well as an extensive battery of neuropsychological tests. Routine laboratory investigations and CT-scan of the brain were also carried out. This information was used by a multidisciplinary medical team to assign a diagnosis to each subject. Various rating scales were used, namely, the Hamilton Depression Rating Scale (HDRS),[53] Reisberg's Global Deterioration Scale (GDS),[54] Blessed Dementia Scale (BDS),[55] Hachinski Ischemic Score (HIS),[51] and the Mini Mental State Examination (MMSE).[56]

Table 6.2. Characteristics of patients and controls

	Alzheimers's disease		Vascular dementia		All patients	
	Patients	Controls	Patients	Controls	Patients	Controls
N of subjects	20	20	20	20	40	40
Age: mean	73.8 (5.5)	73.6 (5.7)	73.3 (6.3)	72.9 (5.4)	73.6 (5.9)	72.9 (5.4)
Age: range	64 - 83	62 - 83	60 - 84	61 - 83	60 - 84	61 - 83
Education	3.2 (1.0)	3.5 (1.2)	3.9 (1.6)	4.1 (1.4)	3.6 (1.4)	3.8 (1.3)
Sex	8M / 12F	8M / 12F	12M / 8F	12M / 8F	20M / 20F	20M / 20F
HIS	2.4 (1.5)	-	9.7 (2.1)	-	6.1 (4.1)	-
BDS	7.3 (3.5)	-	9.4 (4.7)	-	8.4 (4.3)	-
GDS	4.6 (0.7)	-	4.9 (0.7)	-	4.8 (0.7)	-
MMSE	18.0 (4.9)	-	12.9 (5.5)	-	15.8 (5.8)	-
HDRS	7.7 (4.2)	-	8.3 (4.3)	-	8.0 (4.3)	-

Note: For abbreviations see text. Numbers between brackets are standard deviations.

Control subjects were drawn from a large population of subjects who had responded to an advertisement in a local newspaper. These control subjects were normal and healthy according to current criteria used in gerontological research.[57] They were matched to individual patients in the AD group and the VD group in terms of age, sex and level of education. The control subjects underwent a routine physical and neurological examination and a neuropsychological investigation. None of the control subjects had any signs or symptoms of mood or cognitive disturbances. They were paid for their participation. The characteristics of patients and control subjects are given in table 6.2.

There were no differences between patients of the AD and VD groups and the control subjects with respect to the variables age (mean and range), sex and educational level. VD patients were more demented than AD patients as measured by the difference on the MMSE 18.0 and 12.9, GDS 4.6 and 4.9, and BDS 7.3 and 9.4 for AD and VD patients, respectively.

A battery of 8 primitive reflexes (BPR) was used to examine patients and controls. The BPR protocol consisted of a set of guidelines that had been made on the basis of methodological research.[37] In the protocol the subject was told what position to take (e.g., sitting or standing; eyes open or closed, etcetera) were described. No information was given about the nature of the expected response, but the subject was always told about the nature of the stimulus in order to prevent possible startle reactions which might influence the response.

Table 6.3. Example of how reflexes were elicited and scored

Snout reflex

Basic position:	Subject sits straight; the eyes are closed.	
Instruction:	Keep your mouth loosely closed and close your eyes. I will tap your lips a few times with my hammer.	
Stimulus:	Slight tap on the middle of the lips with a reflex hammer.	
Response:	Amplitude	0: no response 1: phasic protrusion of the lips 2: tonic protrusion of the lips, with or without extension of the reflex response
	Persistence	0: no response 1: < 4 consecutive responses 2: ≥ 4 consecutive responses

Every reflex was measured at least three times, with about two seconds between each elicitation, except for the glabellar tap and the nasopalpebral reflexes, which were applied ten times, two times per second. All reflexes were assessed for amplitude and persistence, as proposed by other investigators of PR in adults[42,58–60] and in children.[47] The amplitude and the persistence were scored semi–quantitively on a three-point scale as follows: for amplitude 0= absent, 1= a weak-moderate response, and 2= a strong response; and for persistence 0= absent, 1= response for 1-4 consecutive times, and 2= response for 4 or more consecutive times (persistent). The glabellar tap reflex was considered to be (present but) exhaustible after 4-10 and to be persistent after more than 10 consecutive responses respectively. This is in accordance with the literature,[31,60,61] If appropiate, the reflexes were elicited on both sides. A detailed grading system is published elsewhere.[62] The snout reflex is described in table 6.3 as an example.

6.4 Results

There were more PR per group and more PR per patient in the VD group (table 6.4) than in the AD group, although this difference was not significant. Individual reflexes were detected more often in the VD group than in the AD group, except for the left grasp (equal) and the nuchocephalic reflexes, which occurred slightly more frequently in the AD group. The average number of PR per subject was 4.0 for AD and 5.8 for VD patients, and in their control groups 1.6 and 1.4, respectively. The compound scores for the *nociceptive* reflexes were 2.4 for AD and 4.3 for VD and 0.9 and 1.1 for the control groups. The prevalence of nociceptive signs was significantly higher in the VD group than in the AD group ($p<0.01$). The compound scores for the *prehensile* reflexes were 0.5 for AD and 0.6 for VD, and 0.1 and 0.0 for the controls. The scores of the patient groups were significantly higher than those of the control groups ($p<0.05$). The PR scores for the *remaining* reflexes were 1.2 for AD, and 1.0 for VD, and 0.6 and 0.3 for the respective control groups (both non–significant). See figure 6.1.

The palmar grasp and right nuchocephalic reflexes were not detected in the control groups. In these groups the total number of PR and the nociceptive reflexes were significantly correlated with age. In the VD patients only the total number of PR was correlated with age. This was not so for the AD patients, nor was there any correlation between age in both patient groups and any of the subgroups of reflexes.

Table 6.4. Occurrence of primitive reflexes

		Alzheimer's disease						Vascular dementia					
		Patients			Controls			Patients			Controls		
		N	Abs.	Pres.	N	Abs.	Pres.	N	Abs.	Pres.	N	Abs.	Pres.
Glab		19	15	4	20	16	4	20	8	12	20	17	3
Palm	L	20	11	9	20	17	3	19	5	14	20	16	4
	R	20	12	8	20	18	2	19	6	13	20	18	2
Poll	L	7	2	5	20	19	1	9	0	9	20	17	3
	R	7	3	4	20	20	0	9	0	9	20	17	3
Snout		19	8	11	20	11	9	20	3	17	20	12	8
GrPa	L	19	17	2	20	20	0	20	18	2	20	20	0
	R	19	17	2	20	20	0	20	17	3	20	20	0
Suck		18	12	6	20	18	2	20	13	7	20	20	0
MOFS	L	9	6	3	20	16	4	5	2	3	20	15	5
	R	9	4	5	20	16	4	5	3	2	20	19	1
Nuch	L	19	14	5	20	17	3	15	12	3	20	20	0
	R	19	15	4	20	20	0	15	12	3	20	20	0

Note. See table 6.1 for abbreviations.

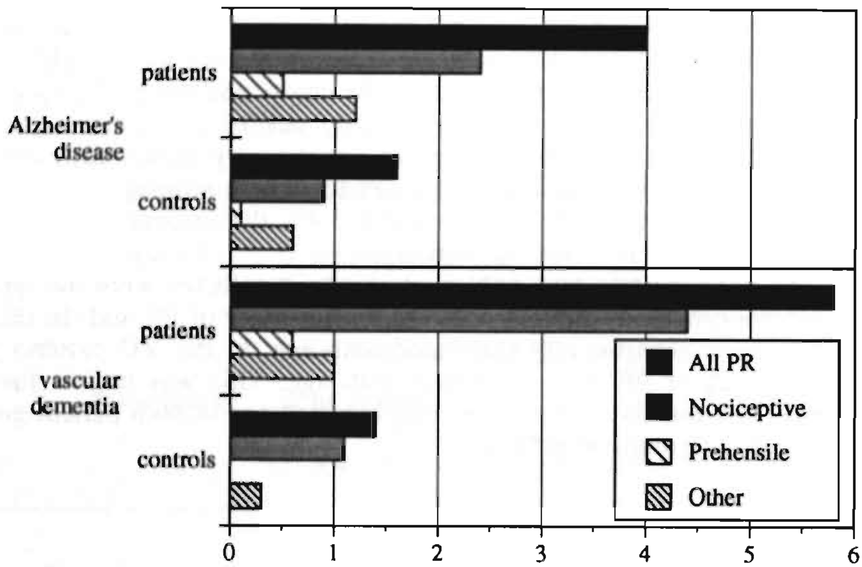

Figure 6.1. Average number of PR in different patient and control groups.

There was no difference in the prevalence of PR between the sexes in the patients or in the control subjects. Nor was there a significant difference between the number of positive reflexes on the left and the right sides, although there was a tendency towards a higher prevalence on the left side in both patient groups and control groups.

In the AD patients 33% and in the control group 12% of all reflexes were positive. The difference between AD patients and their control subjects was particularly evident for the pollico- and palmomental reflexes, and -to a lesser extent- for the suck, the nuchocephalic and the MOFS reflexes. This was in contrast to the findings for the glabellar tap and snout reflexes. The latter reflex was also present in relatively high frequency in the control group. The palmar grasp reflex was rarely found in the AD patients and was not present in the control subjects. There was only a small difference between the persistence of the PR: in the AD group 34% of the PR persisted, but 25% persisted in the control group. See figure 6.2. There was no difference in the amplitude of the

PR between the patient and control groups - virtually all PR were weak to moderate. MMSE correlated well with age and BDS, as did GDS with BDS. There was, however, no correlation between these measures, the HDS and the HIS on the one hand and the total PR or one of the subgroups on the other hand. In the AD group the relationship between the total number of PR was more significant to the'nociceptive' and the 'remaining' reflexes than to the 'prehensile' reflexes.

In the VD patients, 50% and in the control group 11% of all reflexes were positive. There was a remarkably high prevalence of the pollicomental and the palmomental reflexes. The glabellar tap and the MOFS were also detected quite often in the patients. The snout reflex showed a high prevalence in both the patient, and the control groups. The nuchocephalic and the palmar grasp reflexes were unfrequently elicited, but the suck reflex was present in one of three VD patients; these signs were not found in the control subjects. There was a slight difference in the persistence of the PR: 57% and 45% of the PR persisted in the VD and control groups, respectively. See figure 6.3. Again, virtually all responses showed a weak to moderate amplitude in both groups. GDS correlated with total PR. GDS, BDS and MMSE correlated with prehensile signs. Nociceptive signs and total PR were strongly correlated; there was also a correlation between nociceptive signs and education. MMSE correlated well with education, BDS, and GDS. However, there was no correlation between HIS and PR or any of the subgroups.

6.5 Discussion

There is no indication of a basically different PR profile in the two patient groups, indicating that -at least in this stage of the disease- no reflex or combination of reflexes has a diagnostic value for differentiating between the dementing conditions. This is in accordance with the findings of Marterer et al.[34]

Franssen et al.[4] noted that the neurological changes which occur in the earlier stages of Alzheimer's disease may not always be detected on routine testing, but that the problem might to some extent be addressed by rating the observed clinical signs on a scale, and by looking for patterns in groups of individual signs. They found significantly higher scores on summary variables that combined the scores of various individual neurological measures, including PR, already in nondemented subjects with mild memory impairment (GDS 3). The differences that are found in our series between the prevalences of total PR, noceptive, and prehensile signs in AD and VD patients and age-matched controls confirm their findings. The higher numbers of total PR and of nociceptive reflexes in the VD patients compared with the AD patients may

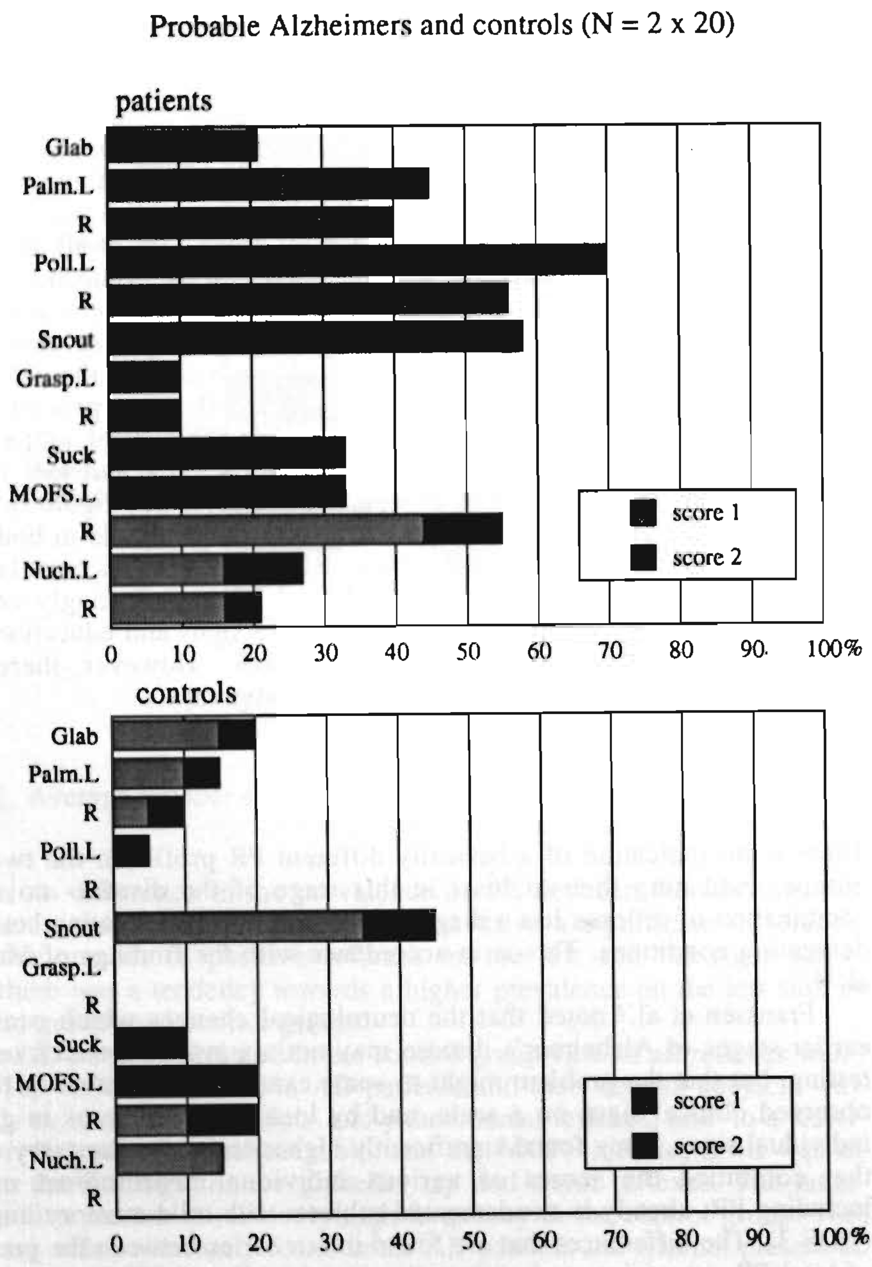

Figure 6.2. Prevalence of PR in probable Alzheimer patients and controls

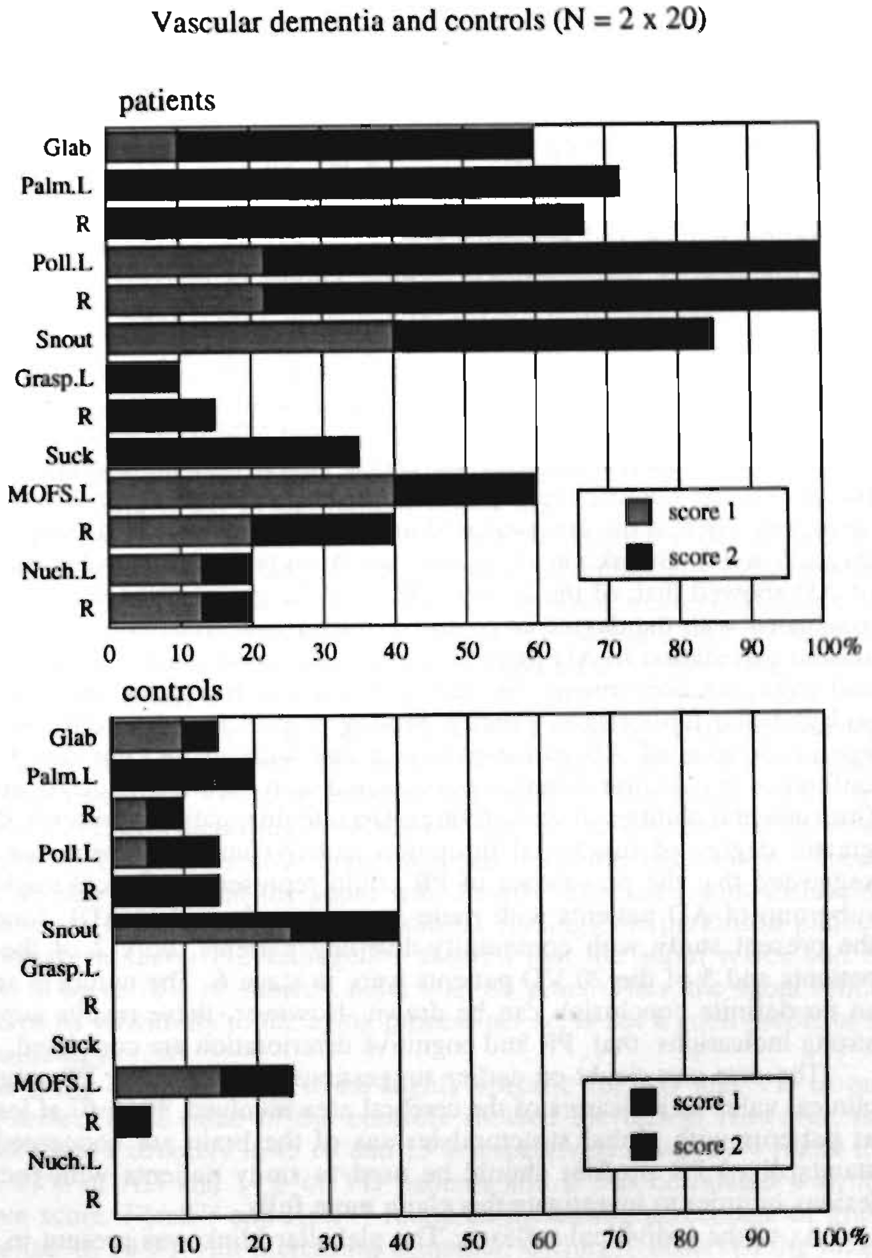

Figure 6.3. Prevalence of PR in patients with vascular dementia and controls

be ascribed primarily to the increased severity of dementia in the VD patients, as measured by lower MMSE and higher GDS and BDS. Our findings are similar to those of Ishi et al.,[6] who reported release signs to predominate in vascular dementia with lacunae, especially in the frontal lobes. Likewise, these signs were found in subjects with diffuse white matter lucencies on computed tomographic scan by Steigart et al.[7] Tweedy et al.[63] reported that the disinhibited snout reflex was observed in 3 of 7 patients with MID. In the review by Jenkyn and Reeves[64] several papers are mentioned in which PR were found to be disinhibited in various groups of patients characterized by 'diffuse cerebral dysfunction'. Whether vascular etiology was prominent in these patient groups is not known.

A clear difference was observed between the prevalence of the prehensile reflexes in both patient groups and the control subjects. The prehensile reflexes showed a relation with GDS, BDS, and MMSE in the VD group, with the prevalence increasing with increasing severity of the disease. Franssen[4] found that the nociceptive signs were more prevalent in the early stages of dementia, whereas the prevalence of prehensile signs increased sharply in GDS stages 6 and 7. Galasko et al[5] in their study on potential neurological markers of AD showed that, of the various PR, only the grasp reflex was significantly associated with the degree of cognitive impairment. Bakchine et al.[10] found a similar association in AD patients between the grasp, suck and snout reflexes and cognitive impairment. No such relation was found for the palmomental and glabellar tap reflexes. Finally, Molloy et al.[14] found no difference in the age or duration of AD in patients with and without PR, nor was there any difference in cognitive function as measured with the MMSE, ADL, and IADL (instrumental abilities of daily living). Despite this, patients with PR showed a greater degree of functional limitation and dysfunctional behavior. Molloy suggested that the prevalence of PR could represent a clinical marker for a subgroup of AD patients with more severe impairment in ADL function. In the present study with community-dwelling patients, only 2 of the 20 AD patients and 5 of the 20 VD patients were in stage 6. The numbers are small, so no definite conclusion can be drawn. However, these results support the strong indications that PR and cognitive deterioration are correlated.

The data cast doubt on earlier suggestions that particular PR might be of clinical value as indicators of the cerebral area involved,[46,65–67] at least as far as patients with global structural lesions of the brain are concerned. Well standardized PR profiles should be used to study patients with focal brain lesions in order to investigate this claim more fully.

As to the individual reflexes: The glabellar blink was present in 21% of the AD patients and in 60% of the VD patients. Pearce[68] reported that 72% of demented patients showed the reflex whereas Koller[27] found that 23 % of AD patients and 8% of controls did. Other studies, e.g., by Huff and Ferguson, indicate that the glabellar blink reflex is among the most prominent release signs.[22,69] This sign was occasionally observed in normal subjects with GDS 1-2 and was more prominent in GDS stages 3-6.[4] The available evidence suggests that the glabellar blink is a release sign which develops quite early.

Similar conclusions apply to two other nociceptive reflexes -the palmomental and the pollicomental reflex. The palmomental reflex is one of the first PR to develop in adult life, according to Ajuriaguerra.[44] Delwaide and Dijeux[70] confirmed this in a longitudinal study on AD patients. Various papers have shown that the palmomental as well as the pollicomental reflex[46] - which has been studied only infrequently- occurs with moderate frequency in nondemented elderly people and in the earlier stages of AD.[4,14,22] Basavaraju et al.[16] found that only the palmomental and grasp reflexes could discriminate between demented and other neurological patients. Recently, in a group comparison study on age-associated memory impairment (Vreeling et al., submitted for publication) it was shown that these two reflexes were present significantly more often in the patient group than in age-matched, healthy control subjects. Reis[71] demonstrated that the palmomental reflex is basically present in all normal individuals, but the presence of a clinically evident reflex suggests a diminution of the cerebral inhibition on lower centers. McDonald[72] found that variability in the palmomental reflex is related to the state of emotionality or anxiety of the subject. More studies are required to assess the relevance of these two reflexes in the elderly.

The snout reflex was found in 60% and 81% in AD patients and VD patients respectively. However, almost half of the control subjects also showed this sign. Tweedy[65] found a relationship between the snout reflex and cognitive decline. According to Koller[20] the snout occurred with equal frequency in AD patients and in age-matched nondemented control subjects (54%); he also found that the snout was directly correlated with increasing age. Gossman and Jacobs[73] reported similar findings for parkinson patients and normal subjects. Hildenhagen[30] showed that the snout reflex can be detected in up to 70% of subjects older than 80 years. Thus, the snout reflex, because of its sensitivity to the aging process per se, is not a good predictor of brain pathology.

The grasp reflex seemed to be highly specific for AD and VD in our patient series, since none of the controls showed the reflex. However, the sensitivity was extremely low: 10 and 15% respectively. Tweedy[63] found the sign in 17% of AD and 14% of VD patients and it was correlated with the cognitive score. Förstl[74] and Huff[22] found an increasing percentage of grasp reflexes (up to 34%) with increasing dementia; Girling[11] observed the reflex in 8 of 24 demented 80-year old people, and Bakchine,[10] who studied AD patients, correlated the reflex to a lower MMSE score. The conclusion is that if a grasp reflex is present and persistent, a hemispherical (frontal?) lesion is probable.

The suck reflex was found in one of three patients and in only two control subjects. As with the grasp reflex, Bakchine[10] found it correlated with the cognitive decline; however, both reflexes were rarely present (7.7% for the suck and 5.5% for the grasp reflex). Richard[75] found this sign to be common in the second of three stages of AD. Again, if present it may indicate diffuse cerebral (frontal?) damage.

The rooting reflex, which was not examined in this study, is of interest in that other prehensile reflexes such as the suck and the grasp reflexes are detected, especially in more severely demented people. The PR may develop in a particular order, with the rooting reflex developing after the suck and grasp reflexes. This interpretation is in line with the 'retrogenesis' theory of de Ajuriaguerra and Hughlings Jackson (see above), and with the findings reported by Delwaide and Dijeux[70] in a longitudinal study of 104 patients with Alzheimer's disease. We plan to study the rooting reflex in future investigations.

Up till now the MOFS has been investigated almost exclusively in children[47, 76, 77]. It has received little attention in research into dementing conditions. However, the results obtained show that it may be of potential interest. The prevalence in AD patients was about 40% and in VD patients even higher: 40% on the right side and 60% on the left side. These figures were about 20% for controls. As the pathogenesis and significance of the MOFS are not yet clear, the high prevalence in the various groups motivates further research.

The nuchocephalic reflex was elicited in over 20% of our patients and in 4% of the controls. Jenkyn[1,45] found this sign only rarely disinhibited in normal adults, its presence increasing with age and in patients with parkinsonism and cognitive impairment. It may serve as an nonspecific sign of diffuse hemispherical disease.

None of the eight reflexes tested has relevance as a possible pathognomonic sign of the disease. Instead, the data indicate that it is important to use compound scores, in which subgroups of PR are formed, in order to increase the sensitivity of the measurement. This yields relevant data, even in the earlier stages of Alzheimer's and vascular dementia; a standardized PR protocol is essential in this respect. PR, measured in a systematic way, may increase our insight into subtle brain dysfunctions which develop in adulthood and senescence.

PR could be elicited throughout the course of AD, including the end stage when cognitive testing results in uniform low bottom scores. The change in type of PR elicited during the early and late stages of AD might make PR useful as independent markers of disease progression and as indicators of potential therapy.[78] PR could also be used in clinical practice and research to identify possible subgroups of AD, as was suggested by Molloy[14] and Neary.[79] This is because reliable categorization of AD patients in subgroups is currently only possible by histological examination; simple clinical tests such as PR would be helpful in this respect. However, Hansen[80] found no difference in the prevalence of three PR between two subgroups of AD patients with and without Lewy bodies. Finally, PR might be useful in the differentiation of AD versus other dementing conditions such as depression.

6.6 Literature

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7 Primitive reflexes in Parkinson's disease

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7.1 Abstract

A standardized protocol for the examination of 15 primitive reflexes (PR) in which the amplitude and the persistence were scored separately, was applied to 25 patients with Parkinson's disease (PD) and an equal number of healthy matched control subjects. Most PR were found considerably more often in the patients than in the control subjects, especially the snout, the glabellar tap, and its variant the nasopalpebral reflex. Only the mouth open finger spread reflex (MOFS) was present more often in the control subjects. For all reflexes except the MOFS, the scores for amplitude and persistence of the reflexes for the control group never exceeded the scores for the patient group. Reflexes persisted more often in the patients than in the control subjects. PD alone can explain a large number of PR, irrespective of the severity or duration of the disease. In contrast, the number of PR was related more to cognitive scales. It is concluded that PR may be helpful in diagnosing PD. In addition, a standardized protocol for eliciting and scoring is essential for the study of these reflexes in parkinsonism and other neuropsychiatric conditions.

7.2 Introduction

The prevalence and clinical value of primitive reflexes (PR) in Parkinson's disease (PD) have been discussed by many authors.[1-4] Although some of these reflexes can be elicited in normal adults[5] and in patients with focal lesions,[6] they are found more often in patients with diffuse, hemispherical disease.[7-10]

In studies on PR in PD, the glabellar tap,[2 3 11 12] the snout,[1 2 10] and palmomental [1 2 4 13] reflexes are especially frequently found. The proportion of glabellar tap, snout, nasopalpebral, suck, and grasp reflexes increases with the severity of PD.[3 8] Findings for the palmomental reflex are controversial.[2 3 13] The presence of PR increases with cognitive impairment.[2 8 10] No relationship has been found between the reflexes and the duration of the disease or the degree of depression of the PD patient.[2 8] In other studies, the incidence of the palmomental and the snout reflexes was not significantly different in patients with Parkinson's disease and healthy age-matched control subjects.[1 5] Though a positive glabellar tap reflex is considered as an important diagnostic sign of PD,[14] it is also found in patients with intracranial disease who do not show any signs of PD, or who show symptoms of a clearly symptomatic parkinsonism.[3 6] In one study, the glabellar tap reflex correlated best with the extent of the lesion and not with the site of the lesion.[3] Several authors have reported the reversal of this reflex in Parkinson patients after therapy with L-Dopa,[11 12 15] amantadine,[11] or lisuride[16]; however, other authors have not confirmed these findings.[1 8] In another study, the palmomental reflex was found to be even more reliable than the glabella reflex as a clinical indicator of PD.[13]

In sum, the findings and conclusions in the literature on PR in parkinsonism are often confusing, controversial, or not readily compatible. This seems not to be due to false diagnoses or to heterogeneity of the patient groups studied, but mainly due to a lack of compatibility of methodology used to elicit and score the primitive reflexes and to the small numbers of -mutually different- reflexes in the various studies.

Recently, we found that experienced neurologists differ considerably in how they elicit and judge PR.[17] The reliable measurement of PR in adult neurological patients therefore requires a very elaborate protocol. A standardized protocol for the study of a 'primitive reflex profile' has not been applied in any of the studies on PR in Parkinson's disease. Most studies have examined only one, and rarely two or three primitive reflexes.[1-3 8 9]

The aim of the present study was therefore to apply a standardized and semi-quantified test battery of 15 primitive reflexes to PD patients in order to determine the prevalence -compared to healthy controls- and the clinical value of these reflexes, by correlating them to parameters such as severity and duration of the disease, cognitive functioning, and depression. The battery that was chosen was found to have high inter- and intra-observer reliability.[17] The following PR are included: the glabellar tap (Glab), palmar and plantar grasp (GrPa and GrPl), palmo- and pollicomental (Palm and Poll), rooting (Root), snout, suck, head retraction (HeRe), nuchocephalic (Nuch), asymmetrical tonic neck (ATNR), mouth open finger spread (MOFS), and palmar and plantar support (SuPa and SuPl) reflexes. Most of these are well-known in research on neurological aging.[7] The last four reflexes have potential value for the use in adults.[18 19] A variant of the glabellar tap reflex, the nasopalpebral reflex (Naso), was added to the battery, because of its presumed clinical value in parkinsonism.[3 20]

7.3 Methods

Subjects.
Twenty-five patients with a diagnosis of idiopathic Parkinson's disease (PD) were selected at random from the neurological outpatient clinic. All had undergone an extensive general and neurological examination, biochemical analysis and CT-scan of the brain, to exclude other causes of parkinsonism. Twenty-five healthy control subjects were matched to the patients with respect to age and sex. See table 7.1 for subject characteristics.

All patients underwent the following examinations: the reflex battery, the Webster rating scale for severity of PD,[21] the Hoehn & Yahr scale for staging of PD,[22] the Global Deterioration Scale (GDS)[23] and the Mini Mental State Examination (MMSE)[24] for assessment of cognitive functioning, and the Zung Depression Scale.[25] The control subjects underwent a neurological examination including the reflexes; none of them showed any neurological sign, or mental deterioration or depression in neurocognitive testing.

Protocol of the primitive reflex battery.
Briefly, a basic position was described and the subject was given instructions as to what was expected of him/her (e.g., sitting or standing; eyes open or closed, etc.). The subject was not informed about the nature of the expected response, but was always informed about the nature of the stimulus in order to prevent

Table 7.1. Characteristics of patients and control subjects

	Patients		Controls	
Number of subjects	25		25	
Age	66.5	(9.5)	67.5	(9.5)
Age (range)	40–84		40–82	
Sex	18 M / 7 F		18 M / 7 F	
G.D.S.	2.0	(0.9)	1.0	
M.M.S.E.	27.4	(2.4)	–	
M.M.S.E. (range)	21–30		–	
Zung Depression Scale	32.6	(8.0)	–	
Hoehn & Yahr	2.3	(0.9)	0	
Webster	11.5	(4.4)	–	
PD since (yrs)	8.0	(6.2)	–	
Diagnosed since (yrs)	6.4	(5.4)	–	

Note: See text for abbreviations. Unless indicated otherwise, mean values are given. Numbers between brackets denote standard deviations.

startle reactions, which might influence the required response. Every reflex was measured at least three times, with about two seconds between each elicitation, except for the glabellar tap and the nasopalpebral reflexes, which were applied two times per second. All reflexes were assessed for amplitude and persistence, as proposed by other investigators of PR.[4 13] If appropriate, the reflexes were elicited on both sides.

Scoring.

Amplitude and persistence of the reflex were scored separately. A three-point scale for both characteristics was used. The scoring was as follows: for amplitude 0 = absent, 1 = a weak-moderate, and 2 = a strong response. A well-defined description for the weak-moderate and strong amplitudes is given for each reflex. For persistence, 0 = absent, 1 = response for 1-4 consecutive times, and 2 = response for 4 or more consecutive times. The glabellar tap and the nasopalpebral reflexes were considered to be (present but) exhaustible after 4-10 consecutive responses and to be persistent after more than 10 consecutive responses respectivily. This is in accordance with the procedure followed by others.[2] A detailed decription of instructions, position, way of elicitation and scoring of each reflex is given elsewhere.[26]

7.4 Results

The prevalence of PR in PD patients and control subjects is shown in the figure. The prevalence increased with age in the control group ($p < 0.01$), but not in the patient group. However, the average number of PR per individual was, irrespective of age, considerably higher in the PD patients than in the control subjects: 4.6 and 0.8 respectivily. For patients younger than 60 years this was 3.9 (0.2), between 60 and 70 years 5.4 (0.5), and for those older than 70 years 3.7 (1.9). There was no difference between males and females.

All but one of the PR occurred more frequently in PD patients than in the control subjects. The over all difference in frequencies per reflex was significant ($p < 0.01$). The glabellar tap and snout reflexes occurred in nearly all patients (96 and 92%, respectively). However, these reflexes were also present in 12 and 20% of the control subjects, respectively. The nasopalpebral reflex, occurred in 88% of the PD patients, but in none of the control subjects. The palmo- and pollicomental reflexes were also found more often in PD patients than in the control group; so were the suck and left nuchocephalic reflexes, albeit to a lesser extent. Only the left MOFS was present more often in the control subjects (20%) than in the PD patients (4%). Six reflexes (ATNR, GrPa, GrPl, HeRe, Root, and SuPl) were absent in both groups.

In the control subjects amplitudes were never scored as 'strong' and only 4 out of 21 responses were persistent (19%). In the patients,the amplitude was

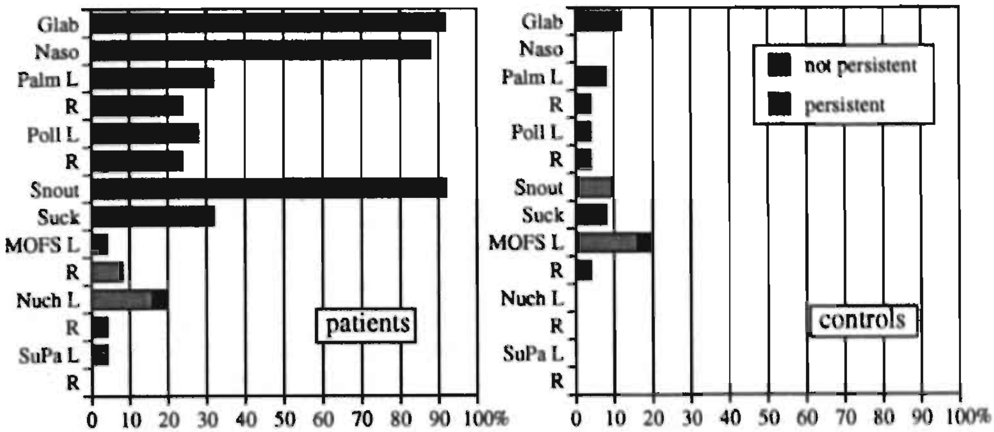

Figure 7.1. Percentage of patients with Parkinson's disease (left) and healthy control subjects (right) showing primitive reflexes.

scored as 'strong' six times, of which four for the snout reflex; however, more than half of the responses (64 out of 118) were scored as 'persistent' (54%). The most frequently persisting PR were the glabellar tap (19/24), the nasopalpebral (11/22), the snout (19/23), and the suck reflexes (5/8). Only the persistence of PR, not the amplitude, was related to the patient group.

The average number of PR did not increase with the duration of the disease, which was estimated retrospectivily after the initial symptoms (range 2-25 years, mean 8.0, SD 6.2), or with the number of years since the diagnosis of PD had been established by a physician (range 1-22 years, mean 6.4, SD 5.4). Hoehn & Yahr and Webster scores were closely related ($p < 0.01$), but did not show a significant correlation with the number of PR. The number of PR increased with the GDS: patients in stage 1-2 (N=18) showed an average of 4.2 PR; patients in stage 3-4 (N=9) showed 5.6 PR ($p < 0.01$). Likewise, MMSE-ratings were weakly related to PR ($p < 0.05$). Depression did not correlate with PR, but it did with the time since the diagnosis of PD ($p < 0.05$) was established. Age did not correlate with the number of PR, but it did –although slightly- with the Webster, Hoehn & Yahr, GDS, and MMSE scores ($p < 0.05$).

7.5 Discussion

Once an individual has definite symptoms of PD, (some) PR show up and they persist. The number of PR does not increase with the duration or severity of the disease. The correlation of PR with the MMSE and GDS is compatible with the view that PR are a sign of diffuse cerebral dysfunction, rather than a symptom of a distinct neurological disease.[3 6 9 10 27]

Our results confirm other findings concerning the most frequently found reflexes. Some state that the persisting glabellar tap sign is probably the best correlative test in Parkinson's disease.[10 14] Gimenez-Roldan et al.[13] found the palmomental reflex an even more reliable clinical indicator. Our results are not in agreement with this, but they do agree on the amplitude and persistence of the palmomental reflex. The (re-)appearance of the nasopalpebral reflex is interesting, from an ontogenetic as well as from a historical point of view.[20] In our study, this reflex seems to have, at least compared to healthy control subjects, an almost equally great sensitivity, and an even greater specificity for PD than the glabellar tap reflex. The snout reflex equals the glabellar sign as to specificity and sensitivity. The asymmetry of the nuchocephalic reflex was not associated with unilateral parkinsonism, in contrast to the palmomental reflex in Maertens de Noordhout's study.[4]

We could not test the negative correlation between the glabellar tap and the palmomental reflexes and dyskinesia reported by Iriarte et al.,[28] since too few patients showed dyskinesia. Concerning the reversal of PR (e.g., the Glab) after starting levodopa, lisuride or amantadine therapy, we could not test this because our patients were on a stable drug regime. Levodopa was taken by 56% of the patients, amantadine by 48%, and the combination of both drugs by 16%. The glabellar sign was present in 96% of our patients, and 79% of these positive responses showed persistence. According to some authors, looking for these reflexes could give an objective, although indirect, evaluation of the patient's dopaminergic status.[4 11 12] However, this was not confirmed by Huber and Paulson.[29] Our findings do not support the view of Messina et al.[11], and Klawans et al.[12] as to the habituation or reversal of the glabellar sign.

The present findings suggest that the glabellar tap, nasopalpebral, and snout reflexes, and especially their persistence, may be of relevance in the examination of PD patients, in view of suggestions that persistence and/or amplitude are correlated with the degree of cerebral degeneration.[2 6 8 10 12 17] A standardized protocol on how to elicit and score PR is required for the study of a broad profile of these signs in neuropsychiatric disorders.

7.6 Literature

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8 Concluding Remarks

This thesis deals with the clinical examination of primitive reflexes (PR) in adults. These reflexes are of use in the assessment of child development, becoming lost in the process of normal brain maturation and demyelinization. To know if they are of any value in the neurological examination of adults requires a scrupulous inventory of the prevalence of these signs in normal, healthy people and comparison of these findings with the results in various patient groups.

In the studies on PR that have been performed up till now, many conflicting results have been found as to the prevalence and significance of these signs, resulting in contradictory conclusions. Some authors are in the belief that PR can be valuable tools in the clinical diagnosis of certain disorders as Parkinson's disease or syndromes as dementia, while others are of the opinion that PR are of no clinical significance whatsoever. It has been stated that PR are strictly localizing signs, and they have been considered unspecific signs of diffuse cerebral disease. In chapter 1, the introduction, and in chapter 2 a survey was given over the sometimes confusing history of the PR that are studied in this thesis. Despite the lack of uniformity in the various studies, an attempt was made to draw a conclusion of what is considered to be the nature and significance of each separate reflex by the majority of the authors so far. It is concluded that the considerable differences of opinion on the clinical value of these signs are caused not only by differences in the number and kind of PR and the patient populations that were studied. The lack of standardization of methodology may play the leading part in the origin of the confusion. Moreover, in the literature, not only different names for the same reflex, but –worse– the same name for different reflexes were found. In conclusion, the confusion seems to be caused by differences in What, on–Whom and How PR were studied. Nevertheless, it is possible to draw some preliminary conclusions from the available literature (chapter 2).

In view of the conflicting methods it was necessary to design a protocol for the examination of PR, that would leave as little as possible room for misinterpretation of how these reflexes should be named, elicited and scored. The studies on PR that have been performed on adults rarely covered a broad specter of PR; moreover, if two or three PR were studied, they differed from study to study. This makes a comparison between the various papers difficult. Therefore, we chose to investigate a 'battery' of 14 reflexes (BPR) for the initial study of healthy volunteers. In this battery not only the reflexes that are usually examined in aging research are present. A number of PR well known in child neurology and of potential use in adults were added. The first protocol that was used by two experienced clinicians showed an excellent agreement on the routine neurological examination, but a very bad agreement on the PR. These results indicated the need for further specification (and they cast doubt concerning data in other papers, where in most studies even a basic protocol is lacking). The second protocol was improved after mutual deliberation and consultation of the volunteers of the first group of healthy young people; the fact that two thirds of them were medical students was of great help in this. The instructions to the examiner and the patient were extended and the way of eliciting and scoring of the PR were defined more precisely. A semiquantitative, separate scoring of both amplitude and persistence of the PR, which in some way had been applied by other investigators –chiefly by child neurologists–, was also introduced in this protocol. Especially the persistence appeared to be of major importance, since the amplitude of the reflexes may vary according to the judgement of the examiner, and also with the mental state of the patient, as -for instance- has been proved for the palmomental reflex. The second protocol, which was applied on 30 and 36 patients resp. with different neurological disorders, showed a good inter– and intraobserver reliability. This was confirmed in satisfying values for weighted kappa, a statistical method to measure agreement on a rating scale that contains a point of absence (chapter 3).

In order to obtain normative data for the prevalence of PR in healthy adults, a cross-sectional study in different age groups was than carried out. A large sample of normal, healthy volunteers, was subdivided into two groups: those with and without biological life events (BLE). BLE are health related factors associated with brain dysfunction, such as mild closed head injury, general anaesthesia etc. In the BLE–free group, at least ten males and ten females in every age group from 20 through 80 years, of both sexes, in all age groups, and of equally divided levels of education, underwent a full neurological examination and were tested with the BPR. The prevalence of PR showed a strong relationship with increasing age, especially the snout reflex was age sensitive. Sex, handedness and level of education were of no influence. Overall, healthy subjects with BLE, in case general anaesthesia and the use of medical drugs, showed more PR than those without BLE; the suck reflex, the only prehensile sign that was found in the whole sample, showed a significant association with BLE. This finding has consequences for the choice of presumably healthy volunteers, in that screening for BLE in the medical history may influence the composition of control groups. Normative data obtained from control subjects could become less reliable if this is omitted. The data obtained in this study may serve as point of departure in studies on PR in the future (chapter 4).

Four groups of neurological patients with cerebral lesions were then examined for PR, following the protocol. The findings of all patient groups were compared with age and sex matched BLE–free control subjects.

A patient group with age associated memory impairment (AAMI) showed a similar pattern as the demented patients, i.e. a high prevalence of nociceptive signs (see chapter 6), though quantitatively less impressive. The prevalence of PR in the patients was significantly higher than in the BLE–free control subjects. Interestingly, there was no significant difference between the totals of PR in AAMI–patients and a control group with BLE in their medical history. However, the PR–profiles of the two groups were different: the (partially persisting) snout, suck, MOFS, and nuchocephalic reflexes prevailed in the controls with BLE, and the snout, palmo– and pollicomental reflexes (largely persisting) were frequently present in the AAMI–patients. It was concluded that the AAMI concept represents a (heterogeneous) group of patients with signs of diffuse cerebral damage, possibly caused by other agents than BLE, their PR profiles suggesting an early phase of dementia (chapter 5).

The snout, palmomental, and pollicomental reflexes were quite frequent in the two groups of demented patients (Alzheimer's and vascular dementia). To a lesser extent the suck, the MOFS, and the nuchocephalic reflexes were found more often in both patient groups than in the controls. The PR profiles of the two groups with dementia were basically similar, perhaps both indicating diffuse cerebral damage by different mechanisms or the possibility of insufficient differential diagnosis between various subgroups of dementia. The subdivision of PR into nociceptive and prehensile signs confirmed earlier findings, stating that the former are mainly present in early dementia, while the latter are prevalent in the more advanced stages of the disease. The numbers of persisting reflexes in both patient groups exceeded those in the control groups, though this difference was not significant (chapter 6).

Patients with idiopathic Parkinson's disease (PD) had a high prevalence (>90%) not only of the glabellar tap and its modification the nasopalpebral reflex, but also of the snout reflex. In view of the combination of the high prevalence of these PR with the fact that the majority of these stable patients used levodopa, our findings did not confirm the statement that PR may disappear with levodopa. In the control group the prevalence of the signs was low (0–12%), so that the combination of these three reflexes may help in the diagnosis of PD. In this study the patients showed considerably more persistent reflexes than the controls (chapter 7).

In all patient groups PR were significantly more often present than in the control groups. The amplitude of the PR was rarely increased in both the patients and the control subjects; the persistence on the other hand was often increased in the patient groups and rarely in the control subjects, indicating that the amplitude of a reflex is of less importance than its mere presence and its persistence. In none of the patient groups a pathognomonic reflex or combination of reflexes was found. However, if some reflexes were clustered, the probability of having some form of brain damage increased considerably. For instance, the nociceptive PR appeared with increasing age, but their prevalence clearly increased in (mild) dementia. The prehensile PR only show up in a very small amount in the very aged controls with BLE, and they clearly tend to increase with deterioration of dementia.

The question has been raised if PR are localizing or pathognomonic signs for disease. In this thesis not one single localizing sign could be distinguished, in view of the fact that no substantial number of patients with small, well–circumscribed lesions were examined. On the other hand, the claim on the specificity of some PR as strictly localizing signs could be denied. For instance, the pollicomental reflex, claimed to be highly (sensitive and) specific for a disturbance in the premotor area (Brodmann 6)[1], was present in some healthy controls as well as in patients without the presumed lesion. As to the question of pathognomy: many neurological (especially degenerative) diseases, are disorders of old age and many PR become more prevalent in senescence. This makes it difficult to distinguish whether one or more PR are signs of disease or mere signs of normal aging. In the present studies the nasopalpebral reflex was the only sign that was present in virtually all (parkinson) patients and in none of the controls. However the number of patients is rather small, and as yet the presence of the reflex has not been examined in other neurological diseases. In general it can be stated that the younger the subject and the more PR she/he shows, the greater the probability for brain pathology. The presence of prehensile signs, especially if they persist, is indicative for pathology, even in the elderly. Clustering of signs, like for instance into nociceptive and prehensile signs, can be of use in the diagnostic process. Making a profile of PR may provide extra information.

As to the origin of PR, the postulate put forward by de Ajuriaguerra[2] in which is stated that the reappearance of PR is the consequence of loss of cortical inhibitory control over lower centers, is based on the Jacksonian concept of a dissolution process of the central nervous system down the ontogenetic scale. In this concept of 'retrogenesis' it would be expected that the reappearance of PR takes place in the reverse order of appearance. De Ajuriaguerra et al. have described grasping and sucking behavior in patients with severe dementia. Paulson and Gottlieb[3] also observed prehensile signs in patients with late–stage dementia. In a longitudinal study on 104 patients with senile dementia by Delwaide and Dijeux[4] the palmomental and glabellar tap reflexes prevailed in the earlier and diminished in the later stages. The suck and grasp reflexes showed up in the late stages. These findings were confirmed in a cross–sectional study by Franssen et al.[5] In their study clustering into nociceptive and prehensile signs proved to be useful. In the present study the nociceptive signs prevailed strongly in the mildly demented patients, whereas the prehensile signs were relatively rare. Despite the low numbers, a significant correlation was found between the severity of dementia and the presence of prehensile signs. The order in which these PR appear in infancy indeed shows that the prehensile signs (the suck, rooting, and grasp reflexes) develop before the nociceptive signs (the glabellar tap, snout, palmo– and pollicomental reflexes), thus providing some support for the postulate above.

With respect to the measurement of PR the following conclusions can be drawn. It has become clear from the confusing data in the literature that a standardized protocol for the examination of PR is a stipulation for the accurate acquirement of reliable data. The protocol in the present thesis has shown to be useful and reproducible. The importance of a subdivision of a semiquantified scoring into amplitude and persistence was demonstrated. In many cases the distinction between patients and healthy controls was visible in the total number of PR. However, the difference was strongly accentuated by a much higher share of persisting reflexes in the total. The differentiation between PR being present solely on the basis of age and pathological PR may be facilitated by the absence or presence of persistence. The examination of PR can be useful when other investigations cannot be applied, e.g., in case of severe agitation. Looking for PR could also be useful in the examination of neuropsychiatric patients and in cases of mild head injury when a routine neurological examination may reveal no abnormalities. When cognitive tests in severe dementia have reached bottom scores, PR can be of use as markers of progression of disease or as indicators of therapy. The latter possibility has already been applied in measuring the efficacy of drug therapy in Parkinson's disease.[6–8]

As to the future: the observations made in this study justify further investigations. Studies with brain imaging and PR are scarce, but of potential importance.[9,10] Large–scale, prospective studies controlled by extensive neuropsychological as well as neurological testing can yield the information necessary to determine the usefulness of PR as markers of cognitive impairment. Large populations will have to be followed for years before the effect of normal aging can be parceled out from that of cortical impairment. If these types of studies are not performed, "these clinical curiosities will continue to tease and please but remain very much the enigmas of the physical examination".[11]

8.1 References

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SUMMARY

This thesis describes some clinical studies of primitive reflexes (PR) in adult healthy volunteers and in various groups of patients.

Chapter 1, the introduction, describes briefly the confusing history of PR in adults, which is at the same time the motive for this study. An overview is given of the many opinions that exist on the various aspects of PR. The different conceptions about what causes the reappearence of these signs, about their clinical value, e.g., as indicators of diffuse cortical damage, of cognitive decline, or as strictly localizing signs are mentioned. The term 'primitive reflexes' is explained and defined for this thesis. The main reasons for the controversies that exist on the prevalence and the clinical value of PR in healthy adults and neurological diseases -a lack of standardization of how to elicit and score these signs- are discussed.

Chapter 2 gives a concise review on the history of 'reflexology' in general, and of fourteen primitive reflexes in particular. Of each separate reflex that was studied in this thesis the first article is mentioned. A short description of how to elicit each reflex and of the response that may be expected is given. The relevant literature for each reflex is reviewed, and its consequences for the present conception of the clinical value of the reflex are discussed.

Chapter 3 discusses the methodological problems in the examination of PR. It reports the results of three studies concerning the inter– and intra–observer reliability of a protocol designed to assess PR in adults. In the first study on healthy young volunteers the interobserver agreement between two neurologists on the routine neurological examination was excellent. However, the agreement on the presence of the (rare) PR was extremely poor, due to lack of an explicit description of the elicitation and scoring of the PR. In the second study a group of 30 neurological patients was examined with an improved, standardized protocol on the methodology of elicitation and scoring of 14 PR. The amplitude and persistence of the reflexes were scored separately, in a semiquantitative way. The interobserver agreement improved considerably, resulting in satisfying kappa values for both amplitude and persistence of the PR. The third study describes the PR findings in 36 neurological patients, who were examined twice by the author within two weeks. The intraobserver agreement was good to excellent. The conclusion was that, since neurologists seem to differ in their way of eliciting and scoring PR, a standardized protocol is required for improvement of the reliability of the results. Such a protocol should contain meticulous descriptions of 1. the position of and the instructions to the patient, and 2. how to elicit and score

the amplitude and persistence of each reflex. The present protocol came up to these expectations.

Chapter 4 presents normative data about the prevalence of 14 PR in 247 healthy adult volunteers. In this study the term 'biological life events' (BLE) emerges. BLE are mild, health related factors that are associated with brain dysfunction (e.g., general anaesthesia, repeated mild head injury, etc.). There were 150 subjects without, and 97 with BLE in their medical history. Males and females were equally divided over both groups. Each group was subdivided into age groups of 20 ± 3 years up to 80 ± 3 years. The prevalence of PR was assessed following the protocol described in chapter 3; besides, all subjects underwent a routine neurological examination. Neurological findings were normal in all subjects. In both groups the prevalence of PR strongly increased with increasing age. The total number of PR increased with BLE, e.g., with general anaesthesia and use of medical drugs. The suck reflex was associated with BLE. In the BLE group some PR showed more often persistence than in the BLE free group. The conclusion from this study was that normative data in research on PR should be regarded with caution, firstly by the lack of standardization of the examination of PR, and secondly by the possible influence of BLE on the prevalence of PR in apparently healthy people. These data can be useful points of departure for futurous studies on PR, serving as standard norms for the prevalence of PR in really healthy people.

Chapter 5 presents a study on the prevalence of PR in patients with age–related memory disturbances. If age–associated memory impairment (AAMI, following the conceptualization of Crook), in some way reflects the presence of – up till now unknown – BLE, and if (an increase in) the prevalence of (some) PR is related to BLE, it were to be expected that the number of PR would be increased in AAMI patients. The prevalence of 8 PR was studied in 15 AAMI patients, and the results were compared with the findings in two matched control groups of 15 subjects each, either affected or unaffected by BLE. The total number of PR and of nociceptive reflexes was significantly higher in the patients and in the control group with BLE than in the BLE free group. Moreover, considerably more reflexes were persistent in the first two groups. AAMI patients may have suffered from certain BLE, as can be inferred from their memory problems, as well as from an increase of PR.

Chapter 6 discusses the clinical usefulness of the PR–profiles in two different forms of dementia, Alzheimer's disease (AD) and vascular dementia (VD). Eight PR that are often mentioned in studies on aging and dementia were examined in 20 AD patients and 20 VD patients. Considerably more PR were found in both patient groups compared with age-matched healthy control subjects. Due to an increased severity of dementia in the VD patients the number of PR in the VD group was higher than in the AD group. However, there was no difference between the PR–profiles of the two diseases. There was a correlation between the prevalence of PR and the severity of the dementia in both groups. Moreover, in the less demented the nociceptive (glabellar tap, snout, palmo– and pollicomental) reflexes prevailed, whereas in the more severely disturbed the prehensile (grasp, suck) reflexes became more prevalent. A pathognomonic reflex or combination of PR could not be distinguished in either group. PR could be helpful in 1) assessing the more severe stages of dementia, when psychometric tests have reached bottom scores; 2) measuring the results of (drug) therapy, and 3. distinguishing different subforms of dementia.

Chapter 7 describes the prevalence of PR in 25 patients with Parkinson's disease (PD). The PR protocol as described in chapter 3 was applied, and the nasopalpebral reflex, a modification of the glabellar tap reflex, was added. The glabellar tap, the snout, and the nasopalpebral reflexes were found considerably more often in the patient group than in age–matched control subjects. This was also true –albeit to a lesser extent– for the palmo- and pollicomental reflexes. The nasopalpebral reflex was not present at all in the control group. This makes this sign even more specific than the glabellar tap sign. The conclusion of this study was that PR, if applied and scored in a standardized way, may be helpful in diagnosing PD.

Finally, in **chapter 8**, a survey is given over the results of the various studies in this thesis. The importance of a thorough neurological examination is stressed and the usefulness of the examination of PR as a part of it is discussed. Some considerations are devoted to future research, especially in the field of PR and aging.

SAMENVATTING

In dit proefschrift worden enkele onderzoeken beschreven naar primitieve reflexen (PR) bij volwassen, gezonde vrijwilligers en bij verschillende groepen patiënten.

In **hoofdstuk 1**, de inleiding, wordt in het kort het verwarrende verleden van PR bij volwassenen, dat tegelijkertijd de aanleiding voor dit onderzoek vormde, beschreven. Er wordt een overzicht gegeven van de vele meningen die er bestaan ten aanzien van de verschillende aspecten van PR. De verschillende inzichten aangaande de oorzaak van de terugkeer van deze verschijnselen en hun klinische betekenis, bijvoorbeeld als aanduiding van diffuse hersenschors-beschadiging, van cognitieve achteruitgang of als nauwkeurig localiserende symptomen worden genoemd. De term 'primitieve reflexen' wordt toegelicht en voor dit proefschrift gedefinieerd. De belangrijkste oorzaken voor de verschillen van mening die er bestaan omtrent de prevalentie en de klinische betekenis van PR bij gezonde volwassenen en neurologische ziekten -het ontbreken van een gestandaardiseerde wijze van opwekken en scoren van deze verschijnselen- worden besproken.

In **hoofdstuk 2** wordt een beknopt historisch overzicht gegeven van de 'reflexologie' in het algemeen en van veertien PR in het bijzonder. Van elke in dit proefschrift onderzochte reflex wordt het eerste artikel vermeld. De wijze van opwekken van iedere reflex en de te verwachten reactie worden kort beschreven. De relevante literatuur aangaande iedere reflex en de gevolgen hiervan voor de huidige opvattingen over hun klinische waarde worden besproken.

In **hoofdstuk 3** worden de methodologische problemen bij het onderzoek van PR bekeken. De resultaten van drie onderzoeken betreffende de inter- en intra-onderzoeker-betrouwbaarheid van een protocol, ontworpen voor de studie van PR bij volwassenen, worden getoond. In het eerste onderzoek bij gezonde jonge vrijwilligers was de interobserver-overeenkomst tussen twee neurologen wat betreft het routine-neurologisch onderzoek uitstekend. De overeenstemming aangaande de aanwezigheid van de (zeldzaam voorkomende) PR was echter zeer slecht, als gevolg van het ontbreken van een expliciete beschrijving van de wijze van opwekken en scoren van de PR. In het tweede onderzoek werd een groep van 30 neurologische patiënten onderzocht met een verbeterd, gestandaardiseerd protocol over de methodiek van opwekken en scoren van 14 PR. Amplitudo en de persistentie van de reflexen werden apart en semi-kwantitatief gescoord. De inter-onderzoekerovereenkomst verbeterde aanzienlijk, wat resulteerde in bevredigende kappa-waarden, voor zowel amplitudo als persistentie van de PR. In het derde onderzoek worden de PR-

bevindingen beschreven bij 36 neurologische patiënten, die binnen twee weken door schrijver dezes werden onderzocht. De intra-onderzoekerovereenkomst was goed tot uitstekend. De conclusie was dat, waar neurologen blijken te verschillen in hun wijze van opwekken en scoren van PR, een gestandaardiseerd protocol nodig is voor de verhoging van de betrouwbaarheid van de bevindingen. Zo'n protocol moet nauwkeurige omschrijvingen bevatten van 1. de positionering van en de instructies aan de patiënt, en 2. de wijze van opwekken en scoren van amplitudo en persistentie van elke reflex. Het huidige protocol beantwoordde aan deze verwachtingen.

In **hoofdstuk 4** worden normatieve gegevens gepresenteerd over de prevalentie van 14 PR bij 247 gezonde volwassen vrijwilligers. Bij dit onderzoek verschijnt de term *biological life events* (BLE). Dit zijn lichte, gezondheid-gerelateerde factoren (bijv. algehele narcose, herhaald licht hersenletsel etc.), die in verband worden gebracht met een gestoorde hersenfunctie. Er waren 150 proefpersonen zonder, en 97 met BLE in de voorgeschiedenis. De man-vrouwverdeling was in beide groepen gelijk. Iedere groep werd onderverdeeld in leeftijdsgroepen van 20 ±3 tot en met 80 ±3 jaar. De prevalentie van PR werd bepaald volgens het in hoofdstuk 3 beschreven protocol; daarnaast ondergingen alle proefpersonen een routine-neurologisch onderzoek. De neurologische bevindingen waren bij allen normaal. In beide groepen nam de prevalentie van PR sterk toe met de leeftijd. Het totale aantal PR steeg met BLE, met name bij algehele anesthesie en gebruik van medicatie. De zuigreflex nam toe bij BLE. In de BLE-groep toonden sommige PR vaker persistentie dan in de groep zonder BLE. De conclusie uit dit onderzoek was dat normatieve gegevens uit onderzoeken op PR met terughoudendheid moeten worden bekeken; ten eerst door het ontbreken van standaardisatie bij het onderzoek van PR en ten tweede door de mogelijke invloed van BLE op het vóórkomen van PR bij ogenschijnlijk gezonde mensen. De huidige gegevens kunnen dienen als uitgangspunt voor toekomstige studies betreffende PR, in de vorm van standaardnormen voor de prevalentie van PR bij werkelijk gezonde mensen.

In **hoofdstuk 5** wordt een onderzoek naar de prevalentie van PR bij patiënten met aan de leeftijd gerelateerde geheugenstoornissen beschreven. Als 'age-associated memory impairment' (AAMI) volgens het concept van Crook, op enigerlei wijze de afspiegeling vormt van –tot nu toe onbekende– BLE, en als (een toename van) de prevalentie van (sommige) PR gerelateerd is aan BLE, dan zou te verwachten zijn dat het aantal PR bij AAMI-patiënten zou zijn toegenomen. Bij 15 AAMI-patiënten werd de prevalentie van de PR onderzocht en de bevindingen werden vergeleken met die bij twee vergelijkbare controlegroepen van elk 15 personen, waarvan één met en één zonder BLE. Het totale aantal PR en het aantal nociceptieve reflexen was significant hoger bij de patiënten en in de controlegroep met BLE dan in de groep zonder

BLE. Bovendien werden in de eerste twee groepen meer persisterende reflexen gevonden. Zowel uit de geheugenproblemen als uit de toename van PR kan worden afgeleid, dat AAMI-patiënten mogelijk onbekende, andere BLE hebben doorgemaakt.

In **hoofdstuk 6** wordt de klinische bruikbaarheid van de PR-profielen bij twee verschillende vormen van dementie -de ziekte van Alzheimer en vasculaire dementie (AD en VD)- besproken. Acht PR die vaak worden vermeld in studies over veroudering en dementie, werden onderzocht bij 20 patiënten met AD en 20 patiënten met VD. Vergeleken met gezonde controlepersonen van dezelfde leeftijd werden in beide patiëntengroepen aanzienlijk meer PR gevonden. Op basis van de ernstiger dementie van de VD-patiënten was het aantal PR in de VD-groep groter dan in de AD-groep. Er was echter geen verschil in de PR-profielen van de twee aandoeningen. Tussen de prevalentie van PR en de ernst van de dementie bestond in beide groepen een correlatie. Bovendien kwamen de nociceptieve (glabella tap, snout, palmo- en pollicomentale) reflexen vaker voor bij de minder demente patiënten, terwijl bij de ernstiger gestoorde patiënten de prehensiele (grijp, zuig) reflexen frequenter werden. In geen van beide groepen werd een pathognomonische reflex(combinatie) gevonden. PR zouden van nut kunnen zijn bij 1) het beoordelen van de diepere stadia van dementie, wanneer psychometrische testen bodemscores hebben bereikt, 2) het meten van de resultaten van (medicamenteuze) therapie, en 3) het onderscheiden van verschillende subvormen van dementie.

In **hoofdstuk 7** wordt de prevalentie van PR beschreven bij 25 patiënten met de ziekte van Parkinson (PD). Het PR protocol, zoals beschreven in hoofdstuk 3, werd gebruikt en de nasopalpebrale reflex, een variant van de glabella tapreflex werd toegevoegd. De glabella tap, de snout en de nasopalpebrale reflexen werden aanzienlijk vaker in de patiëntengroep gezien dan in de controlegroep van overeenkomstige leeftijd. Dit was ook het geval –echter in mindere mate– bij de palmo- en pollicomentale reflexen. De nasopalpebrale reflex werd in de controlegroep in het geheel niet gevonden. Dit maakt deze reflex zelfs specifieker dan de glabella tapreflex. De conclusie uit deze studie was dat PR, indien uitgevoerd en gemeten op een gestandaardiseerde wijze, een bijdrage kunnen leveren in de diagnostiek van de ziekte van Parkinson.

In **hoofdstuk 8** wordt tot slot een overzicht gegeven van de resultaten van de verschillende studies in dit proefschrift. Het belang van een grondig neurologisch onderzoek wordt benadrukt en het nut van het onderzoek op PR als deel daarvan wordt besproken. Enige beschouwingen worden gewijd toekomstig onderzoek, vooral op het vlak van PR en veroudering.

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CURRICULUM VITAE

De schrijver van dit proefschrift werd op 23 april 1943 te Velsen geboren. Hij bezocht het Lorentz Lyceum te Haarlem, waar hij in 1960 het diploma hbs-b behaalde. De studie geneeskunde in Utrecht werd in 1968 met het doctoraal-examen afgerond. Van 1966-1968 was hij als student-assistent werkzaam bij de afdeling Anatomie (prof. dr. W.J. van Doorenmalen). De co-assistentschappen, inclusief drie maanden 'vakantie-assistentschap' interne geneeskunde, werden alle onder auspiciën van de stichting Klinisch Hoger Onderwijs in Rotterdam doorlopen, waar in 1970 het artsexamen werd afgelegd. Gedurende enkele maanden werd vervolgens waargenomen in de praktijk van een van de twee Rotterdamse havenartsen. De opleiding tot militair districtspsychiater (DP) vond plaats bij de SGGZ in Den Haag (dr. R. Somers), waarna de resterende diensttijd werd uitgediend als DP van het district Zuid-Nederland. Aansluitend volgde van 1972-1976 in het Academisch Ziekenhuis Dijkzigt te Rotterdam de opleiding tot neuroloog (prof. dr. A. Staal, voor de stage psychiatrie prof. dr. G.A. Ladee). Na een waarneming van vier maanden in het Clara-ziekenhuis te Rotterdam werd in 1977 de aantekening klinische neurofysiologie behaald (prof. dr. M. de Vlieger). Sinds 1 januari 1978 is schrijver dezes als staflid verbonden aan de vakgroep Neurologie van het Academisch Ziekenhuis Maastricht.

Appendix: Protocol on the examination of primitive reflexes

The protocol described in the appendix was published earlier as report:
Vreeling, F. W., Verhey, F. R. J., & Jolles, J. (1987). *Protocol on the examination of primitive reflexes*. Protocol 87-0126. University of Limburg. Depts. of Neurology & Neuropsychology and Psychobiology.

Introduction

The detailed description of elicitation and scoring on the following pages is the result of mutual consultation between the first two authors to arrive at consensus. As was described in chapter 3, little or no unanimity existed as to the presence of PR in healthy subjects, examined by the same observers at separate occasions. This warranted a much more detailed description. Also described in chapter 3, with the present protocol good to excellent inter-observer reliability can be reached. Obviously, the authors had reached agreement (the basis for this protocol) so that this reliability does not necessarily extend to other observers. However, since then, numerous colleagues have used this protocol, both in clinical use and for research purposes. In the majority of these cases agreement –between the examiners and with the authors– is very high. Presently, a subset of the PR discussed here (those with the highest prevalence) is studied in the Netherlands's Memory and Aging Program (NMAP). This is a longitudinal study involving very large numbers of healthy subjects, with ages ranging from twenty-five to eighty at the start of the project. Also, all patients in the Maastricht Memory Clinic (MMC) are examined with this battery.

Before the elicitation of a reflex the subject is instructed as to what is expected of him/her (basic position, eyes open or closed etc.) and what stimulus is to be expected. This is done in order to prevent possible startle reactions, which might influence the response. No information is given as to the nature of the expected response.

Every reflex is measured four times, with about two seconds between every elicitation, except for the glabellar tap and nasopalpebral reflexes, which are elicited ten consecutive times at two times per second. If appropriate, the reflexes are elicited on both sides and scored separately.

All reflexes are judged on the criteria of amplitude and persistence. A three-point scale for both characteristics is used, except for the amplitudes of the glabellar tap, head retraction, nuchocephalic, and nasopalpebral reflexes, which are scored as absent or present.

For amplitude, scoring is as follows:

0 = absent 1 = weak to moderate amplitude 2 = strong amplitude. (A description of the scores for amplitude is given for each reflex separately.)

For persistence:

0 = absent 1 = <4 consecutive responses (CR) 2 = 4 or more CR

Scoring of the persistence of the glabellar tap and the nasopalpebral reflexes:

0 = <4 CR 1 = 4 –10 CR 2 = ≥10 CR

Thus, each reflex is scored with a two digit code, the first digit being the score for the amplitude and the second for the persistence. For instance, score (1.2) means that a certain reflex shows a weak-moderate amplitude, and that it is persistent. The reflex is scored negative (0.0) for both amplitude and persistence when no response is found at all, except for the glabellar tap and nasopalpebral reflexes (v.s.). A negative score for a particular reflex is not changed when the response is found positive after another stimulus (e.g., a grasp reaction measured upon stimulation for the palmomental reflex). The scoring is conservative: any doubt as to the presence will result in a score 'not present'.

1. Asymmetric tonic neck reflex (ATNR)

Basic position	The subject is supine, the arms are flexed slightly; the hands are placed on the thighs (in neutral position, between supination and pronation). In case of a positive response restore basic position.
Instruction	Relax and close your eyes. I will turn your head to the left and the right a few times.
Stimulus	The subject's head is turned to each side, four times in succession.
Response	Amplitude 0 = no response (NR) 1 = increase of muscular tone in the arm and/or leg to which the face is turned and/or decrease on the opposite side. 2 = extension of the arm and/or leg on the side to which the face is turned and/or flexion of the arm and/or leg on the opposite side Persistence 0 = NR 1 = fewer than 4 consecutive responses (CR) 2 = 4 or more CR

2. Glabellar tap reflex (Glab)

Basic position	The subject either sits up straight or is supine.
Instruction	Look straight ahead, fix your gaze on .... (If possible, the examiner should indicate a fixation point.) I will tap your forehead with my reflex hammer.
Stimulus	The glabellar region is tapped gently with a reflex hammer, about two times per second. The forehead is approached from above to prevent visual stimuli from eliciting a response.
Response	Amplitude 0 = NR, or fewer than 4 CR 1 = blinking with each tap. The eyes do not have to close; minimal reactions are not scored Persistence 0 = fewer than 4 consecutive blinks 1 = 4-10 consecutive blinks 2 = 10 or more consecutive blinks.

3. Grasp reflex, palmar (GrPa)

Basic position	The subject sits up straight; the hands are relaxed, palm upwards, in the lap.
Instruction	Relax your hand, do not hold on. If the subject grasps at the first stimulus, repeat the instruction.
Stimulus	The surface of the palm is stroked, in a proximal to distal direction, by the examiner with his/her index and middle fingers.
Response	Amplitude 0 = NR 1 = flexion of the fingers, with or without the thumb, without the subject holding the examiner's fingers. 2 = as above, but the subject holds the examiner's fingers. Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

4. Grasp reflex, plantar (GrPl)

Basic position	The subject is supine, the legs are stretched.
Instruction	Relax, you do not have to do anything.
Stimulus	Pressure is applied to the ball of the foot with a spatula.
Response	Amplitude 0 = NR 1 = curling of the toes 2 = curling of the toes, with wrinkling of the sole of the foot and flexion and adduction of the toes. Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

5. Head retraction reflex (HeRe)

Basic position	The subject sits up straight with the head bent slightly forward; the eyes are closed.
Instruction	I will tap you lightly on the mouth; you do not have to do anything.
Stimulus	The middle of the upper lip is tapped lightly with a reflex hammer.
Response	Amplitude 0 = NR 1 = a brisk backward jerk of the head Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

6. Mouth Open Finger Spread Reflex (MOFS)

Basic position	The subject stands up straight, the eyes are closed and the arms hang loosely by the sides.
Instruction	When I say "yes", open your mouth as wide as possible as quickly as you can, and keep it open.
Stimulus	The patient opens his/her mouth wide as quickly as possible on hearing the command "yes".
Response	Amplitude 0 = NR 1 = distinct spreading of the fingers without extension of the thumb or fingers. 2 = spreading and extension of the thumb or fingers Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

7. Nuchocephalic reflex (Nuch)

Basic position	The subject stands up straight; the eyes are closed. The examiner stands behind the subject and places his/her hands on the subject's shoulders.
Instruction	Relax, you do not have to do anything. I will turn your shoulders to the left and right. Keep your eyes closed.
Stimulus	The patient's shoulders are turned briskly to each side, four times in succession, and kept in the position for 2 seconds.
Response	Amplitude 0 = the patient turns his/her head in the same direction as the shoulders after a lag of about half a second. 1 = the head holds its original position Persistence 0 = the head always turns in the direction of the shoulders 1 = the head does not always turn in the direction of the shoulders, fewer than 4 CR 2 = the head does not turn in the direction of the shoulders, 4 or more CR

8. Palmomental reflex (Palm)

Basic position	The subject sits up straight; the hands are relaxed, palm upwards, in the lap.
Instruction	Relax, you do not have to do anything. Keep your eyes closed. I will scratch your hands.
Stimulus	The thenar is scratched briskly, in a proximal to distal direction, with a blunt object (Yale key).
Response	Amplitude 0 = NR 1 = distinct contraction of the ipsilateral mentalis muscle, without movement of the chin 2 = bilateral contraction of the mentalis muscle and/or movement of the chin Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

9. Pollicomental reflex (Poll)

Basic position	The subject sits up straight; the hands are relaxed, palm upwards, in the lap.
Instruction	Relax, you do not have to do anything. Keep your eyes closed. I will scratch your thumbs.
Stimulus	The distal phalanx of the thumb is scratched briskly, in a proximal to distal direction, with a blunt object (Yale key).
Response	Amplitude 0 = NR 1 = distinct contraction of the ipsilateral mentalis muscle, without movement of the chin 2 = bilateral contraction of the mentalis muscle and/or movement of the chin Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

10. Rooting reflex (Root)

Basic position	The subject sits up straight; the eyes are closed.
Instruction	Relax your lips and keep your eyes closed; you do not have to do anything. I will touch your cheek.
Stimulus	The corner of the mouth is touched lightly with a spatula.
Response	Amplitude 0 = NR 1 = opening of the lips and turning of the lips or head towards the stimulus 2 = swallowing and sucking or biting of the spatula. Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

11. Snoutreflex (Snout)

Basic position	The subject sits up straight; the eyes are closed.
Instruction	Keep your mouth loosely closed and your eyes closed. I will tap your lips.
Stimulus	The middle of the upper lip is tapped lightly with a reflex hammer.
Response	Amplitude 0 = NR 1 = phasic protrusion of the lips 2 = tonic protrusion of the lips, with or without extension of the reflex response. Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

12. Suck reflex (Suck)

Basic position	The subject sits up straight; the eyes are closed.
Instruction	Keep your mouth slightly open but your eyes closed. I will touch your lips. You do not have to do anything. When biting, sucking etc. occurs: repeat the instruction.
Stimulus	A spatula is placed between the subject's lips and moved slowly to and fro, for 2 seconds.
Response	Amplitude 0 = NR 1 = sucking 2 = sucking with swallowing and/or biting Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

13. Support reflex, palmar (SuPa)

Basic position	The subject is supine; the arms are not completely stretched and the hands are positioned with palms upwards.
Instruction	I will push your hand. Do not do anything.
Stimulus	The examiner briskly pushes the patient's hand in dorsiflexion while supporting the patient's arm. The arm is bent slightly at the elbow.
Response	Amplitude 0 = NR 1 = non-fixed extension of the elbow joint 2 = fixed extension of the elbow joint Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 ore more CR

14. Support reflex, plantar (SuPl)

Basic position	The subject is supine; the legs are stretched.
Instruction	I will push your foot. Relax, you do not have to do anything.
Stimulus	The examiner briskly pushes the patient's foot in dorsiflexion while supporting the patient's leg at an angle of about 30° to the bed. The leg is bent slightly at the knee.
Response	Amplitude 0 = NR 1 = non-fixed extension of the knee joint 2 = fixed extension of the knee joint Persistence 0 = NR 1 = fewer than 4 CR 2 = 4 or more CR

15. Nasopalpebral reflex (Naso)

The Naso is a variation of the glabellar tap reflex. It was elicited as such in the group of patients with Parkinson's disease (chapter 8).

Basic position	The subject either sits up straight or is supine.
Instruction	Look straight ahead, fix your gaze on .... (If possible, the examiner should indicate a fixation point.) I will tap your nose with my reflex hammer.
Stimulus	The point of the nose is tapped gently with a reflex hammer, about two times per second. The nose is approached from below to prevent visual stimuli from eliciting a response.
Response	Amplitude 0 = NR, or fewer than 4 CR 1 = blinking with each tap. The eyes do not have to close; minimal reactions are not scored Persistence 0 = fewer than 4 consecutive blinks 1 = 4-10 consecutive blinks 2 = 10 or more consecutive blinks.

In this thesis a study on primitive reflexes (PR) in adults is presented. A standardized protocol on the examination and scoring of fourteen PR was designed. After a thorough revision, it proved to have sufficient inter- and intra-observer reliability. In order to obtain normative data for the prevalence of PR in adults, the protocol was then applied to a large number of healthy volunteers, with ages ranging from 20 to 80 years. The volunteers were subdivided into groups with and without 'biological life events' (BLE). These are health-related factors such as general anaesthesia or mild head trauma, associated with brain dysfunction. The prevalence of PR increased with age. Furthermore, the number of PR in the subjects with BLE was higher than in those without. This was also true for a group of patients with age associated memory impairment (AAMI). Examination of PR in two groups of patients with dementia -Alzheimer's disease and vascular dementia- revealed an increased prevalence of most PR, associated with the severity of dementia. The nociceptive signs prevailed in the early stages of dementia, whereas the prehensile signs came up in the later stages. The 'PR-profiles' of both groups were basically similar. PR might 1. be helpful in the assessment of the more severe stages; 2. serve as measuring tools for therapy; 3. help in distinguishing other (sub)forms of dementia. Finally, in a group of patients with idiopathic Parkinson's disease (PD) the glabellar tap, nasopalpebral, and snout reflexes were found in about 90% of the patients and much less so in the control subjects. Therefore, these PR may be helpful in diagnosing PD.

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