GENERAL DISCUSSION
The present thesis has extended our knowledge on night blindness and may contribute to well founded assistance and advice to patients with night blindness. In the following, I will summarize the studies, their main outcome and value for the field of ophthalmology and low vision rehabilitation. Furthermore, I will describe unresolved questions and other problems that remain for patients with night blindness.

The 15 Hz ERG studies

The 15 Hz ERG studies described in Chapter 2 and Chapter 3 resulted in a 15 Hz ERG protocol that can be used to investigate the functioning of the primary and secondary rod pathways in patients. 15 Hz ERGs are known to show a minimum in amplitude versus intensity curves where the primary and secondary rod pathway destructively interfere. At intensities below and above that of the minimum, the primary and secondary rod pathways dominate, respectively. However, it was unclear at what intensities the cone pathway also becomes active. In the first study, we investigated the origin of the 15 Hz signals and the contribution of the cone system in healthy subjects, using properties for which the rod system deviates from the cone system. These characteristics were spectral sensitivity and temporal frequency sensitivity. The stimuli were varied in colour (blue, green, amber, and red) and in flash duration (short flash and square wave). We found that at low intensities, including the intensity of the first minimum, the rod system dominates. At high intensities we found a second minimum. At intensities above the second minimum, the cone system dominates. This study clarified at which intensities contributions of the cone system can be expected, which is important for the interpretation of abnormal 15 Hz ERGs in patients. The 15 Hz ERG protocol that we recommend generates both minima in healthy subjects. These minima distinguish signals that are dominated by the primary rod pathway, the secondary rod pathway, and the cone pathway, respectively.

In the second study, we applied the protocol in 20 healthy subjects to determine normal ranges. We also applied the protocol in an achromat and in CSNB patients. These measurements confirmed our interpretation of the signals: in the achromat, the signals were normal at low intensities and we found a first minimum. However, at the intensity
of the second minimum, the signals did not increase but instead diminished completely. This suggested that the two rod pathways functioned normally, while the cone pathway was functionally absent. In the CSNB1 patients, signals appeared only at high intensities and no minima could be recorded. This indicated that the cone pathway functioned normally while both rod pathways were functionally absent. The ERGs of the CSNB2 patients showed secondary rod pathway signals and cone pathway signals (a “second” minimum), while signals from the primary pathway were either too small to be recorded or completely absent (no “first” minimum). This study showed that the proposed 15 Hz ERG protocol can be used to examine the functions of the primary and secondary rod pathways in patients. Because we can distinguish signals from the cone pathway, these signals do not interfere with rod pathway examinations.

One question that remains unanswered in these studies is whether we measure signals from both the ON and OFF pathways. As shown in Figure 1.3 of the introduction, both the primary and secondary rod pathways can use the ON and OFF system (ON1, OFF1, ON2, OFF2). However, it is unclear whether ON and OFF pathways are equally active, and whether ON and OFF pathway signals are both recorded on ERG. It is known that the ON pathways transport signals generated upon the increment of light, while OFF pathways transport signals induced by the decrement of light in a lighted area of the retina. It is tempting to think that, in darkness, the contributions of the OFF pathways are less significant. On the other hand, the fact that rod OFF pathways exist, points to at least some usefulness.

As mentioned in the Introduction, a third rod pathway exists (Figure 1.3, OFF3). Zeitz et al. recorded 15 Hz ERGs in CSNB1 patients with GRM6 mutations. They found differences between the 15 Hz ERGs of GRM6 patients and other CSNB1 patients (mutations in NYX or TRPM1). The different 15 Hz ERGs of the GRM6 patients indicated interference of signals from the third rod pathway. However, these signals only showed a high amplitude in two young GRM6 patients, while the signals recorded in two older GRM6 patients had a very low signal to noise ratio. The reason for this discrepancy is unclear. During the course of this project, we did not encounter new GRM6 patients.
Symptoms and genetic causes of CSNB

In Chapter 4 we showed that mutations in the TRPM1 gene cause CSNB1. In previous studies it was found that the modulation of TRPM1 leads to a change in the membrane potential of ON bipolar cells, thus making TRPM1 essential for ON bipolar cell function. In our study, we found that TRPM1, like the other CSNB1 genes, was localized on rod ON bipolar cell dendrites. In addition, six of our patients with the CSNB1 phenotype had mutations in the TRPM1 gene. Due to this research, we know more about the proteins...
that are involved in the signalling transfer through the retina. Furthermore, knowing the
geneic cause of a patient’s disorder finalizes the diagnosis.

For the study on CSNB described in Chapter 5, we collected the clinical and
electrophysiological data of 101 Dutch CSNB patients. This study comprises the largest
group of CSNB patients described in literature to date. There are several reasons why
Bartiméus has gathered such a large cohort of CSNB patients. First of all, Bartiméus
has become an expert institute on congenital retinal eye diseases and electrophysiology.
Therefore, ophthalmologists from all over the country refer young patients to Bartiméus
for diagnosis. Furthermore, with the expansion of the CSNB patient group, it became
clear that the CSNB symptoms are highly diverse. This, in turn, caused an increase in
considering CSNB as a diagnosis in new patients and in the number of patients diagnosed.

As mentioned before, the CSNB diagnosis is primarily based on the electronegative ERG.
The subsequent distinction between CSNB type 1 and type 2 is based on the elevation
of the DA curve, and the scotopic and the photopic ERGs. In our study, we found that
the photopic ERG was the most specific criterion to distinguish between CSNB1 and
CSNB2, as it showed a ‘square wave’ appearance in CSNB1 and a decreased b-wave in
CSNB2. Our study included 39 CSNB1 patients and 62 CSNB2 patients. In 36 CSNB1
patients and 58 CSNB2 patients, the electrophysiological diagnosis of either CSNB1 or
CSNB2 was confirmed by DNA analysis, as a disease causing mutation was found in one
of the CSNB1 genes or one of the CSNB2 genes. This result shows the effectiveness and
value of electrophysiology in diagnosing CSNB. Furthermore, the missing mutations in
seven CSNB patients may indicate yet unidentified CSNB disease genes.

Symptoms that are typically associated with CSNB are: night blindness, myopia,
hyperopia, nystagmus and a decreased visual acuity. We investigated these symptoms in
39 CSNB1 patients and 62 CSNB2 patients. Night blindness was present in all CSNB1
patients, but in only about half of the CSNB2 patients. Remarkably, about 20% of the
CSNB1 patients and about half CSNB2 patients were photophobic. About 75% of the
CSNB1 patients were highly myopic (>-6D), compared to only 50% of the CSNB2
patients. One quarter of the CSNB2 patients was hyperopic. Nystagmus was found in about 70% of both the CSNB1 and CSNB2 patients. Strabismus was present in about 60% of the CSNB1 patients and in about 40% of the CSNB2 patients. The CSNB2 patients had on average a significantly more decreased visual acuity compared to the CSNB1 patients. Some of the CSNB1 patients even had a (near) normal visual acuity. Furthermore, we found that none of the typical symptoms were present in all patients. Overall, we found relatively good visual functions in the CSNB patients. Still, our group may be biased to the more severe cases, as CSNB patients with minor visual problems may never consult an ophthalmologist, or even less likely visit a low vision rehabilitation centre, unless actively referred to by an ophthalmologist.

CSNB is considered to be a predominantly X-linked inheriting disorder. The first two genes associated with CSNB were NYX (CSNB1) and CACNA1F (CSNB2) which are both localized on the X-chromosome. Our study showed that, indeed, most CSNB2 patients had CACNA1F mutations. Only three CSNB2 patients had mutations on the CABP4 gene with autosomal recessive inheritance. In contrast, about half of the CSNB1 patients had mutations in autosomal recessively inherited genes: TRPM1, GRM6, or GPR179. Thus, CSNB is not a disorder that occurs almost exclusively in males. This is an important message for pediatric ophthalmologists and geneticists. Furthermore, we found that, despite the different genetic causes, all CSNB1 patients show the same unique CSNB1 phenotype. In contrast, CSNB2 caused by mutations on either CABP4 or CACNA1F may cause different phenotypes. We examined only three CABP4 patients, but they all showed a phenotype with merely cone-related problems, while CACNA1F patients show both cone- and rod-related problems. Finally, we compared patients with similar CACNA1F mutations. We found that the phenotypic differences among these patients were comparable to the phenotypic differences among CACNA1F patient with different mutations. This suggests that the CSNB phenotype is not only determined by the causative mutated gene, but also by other genetic or environmental factors.

Night Blindness

In the study on CSNB (Chapter 5), we reported on the presence or absence of night
blindness symptoms in CSNB patients. We based this report on the history taking during clinical examination, where we asked patients if they experienced night blindness. This question was answered with either “yes” or “no”, no extensive questionnaire on night blindness was available. We furthermore reported on the results of the DA curve, but the correlation between the dark adapted threshold and night blindness had never been investigated. Because no set of tests was available to qualify a patient’s scotopic visual functions, and because night blindness has never been thoroughly investigated in CSNB patients, we performed a first exploratory study on night blindness in CSNB (Chapter 6). We developed a questionnaire based on two existing questionnaires and our own experience. This questionnaire may be used for future investigations of the night blindness experience of patients with different retinal disorders. Furthermore, we measured the conventional DA curve, but also developed two other scotopic function tests. We measured scotopic visual fields, for which we adapted standard tests from the Octopus perimeter. We furthermore developed a two dimensional version of the Light Lab. In this test, a digital image of a living room with objects is projected on a screen. While increasing the intensity of the image, we asked the patients to report on detection and recognition of objects. With these three functional tests we were able to measure, (1) the absolute threshold for a dim white stimulus, (2) the scotopic visual field, and (3) detection of objects at several light intensities, which is clearly an extension on available scotopic visual function tests. However, more research is needed to show the clinical value of these tests in patients with retinal diseases other than CSNB. Maybe different tests may retrieve more valuable information, for instance, scotopic visual acuity, sensitivity for moving objects, or changes in contrast sensitivity.

For the CSNB2 patients, results from the questionnaire showed that they hardly experience any night vision problems. Furthermore, their DA curves were only slightly elevated, their scotopic visual fields were relatively intact with slightly increased thresholds, and also the results from the light lab were close to normal. However, there were differences between patients; in some patients the scotopic functions were more impaired. Overall, the scotopic visual functions were hardly affected in CSNB2 patients. For the CSNB1 patients, the results from the questionnaire showed that they did experience night vision
problems, although they generally did not describe them as severe. The scotopic visual functions were very similar in CSNB1 patients and more severely affected than in CSNB2 patients. As in CSNB2, the CSNB1 patients had relatively normal visual fields, just above their dark adapted thresholds. The results from the “2D Light Lab” showed that all CSNB1 patients were blind at low intensities (equal to starlight), but quickly recovered at higher intensities (full moonlight). As in the industrialized world streets are usually well-illuminated at night, their overall problems appear not to be very disabling.
THE NAME OF THE DISORDER CSNB

The study on night blindness in CSNB patients improved our knowledge on their scotopic visual functions and their possible problems at night. Because of this, we can give better advice to CSNB patients and parents of young CSNB patients. For instance, we can now advise parents of young patients that it is possible to let their child cycle to school when it is dark, as long as it takes well lighted streets and uses an adequate head lamp. Unfortunately, there remains one major obstacle in adequately informing and advising CSNB patients or their parents, and that is the name of their disorder. Actually, the problem is twofold. First of all, the disorder is called “congenital stationary night blindness”. Because of this name, it is very hard for parents of CSNB patients to understand and believe that their child may not be blind at night. Understandably, it may make them think twice before they let their child ride a bike to school when it is dark outside, with the result that the independence of the child is hampered. Thus, the name CSNB introduces an un-called for participation limitation.

Secondly, we distinguish CSNB type 1 and type 2. More conventionally, these types are called “complete” and “incomplete” CSNB, respectively. These terms reflect on the severity of night blindness in the patients: scotopic visual functions of patients with CSNB1 or “complete” are more impaired than in CSNB2 or “incomplete” CSNB patients. However, patients and parents often interpret these names as a reflection of the overall impairment of visual functions. In daily life (school/work), patients will most frequently encounter problems because of their decreased visual acuity. As shown in this thesis, the visual acuity is significantly better in “complete” CSNB (CSNB1) patients compared to “incomplete” CSNB (CSNB2) patients. Thus, CSNB2 patients will most likely experience more visual problems in daily life than CSNB1 patients. Again, rehabilitation centres have to explain patients that they are not “better off” having “incomplete” CSNB, compared to “complete” CSNB.

The dual naming problem in CSNB shows that bad terminology stands in the way of rehabilitation and the patients coping with the disorder. The terms “complete night
blindness” and “incomplete night blindness” refer to a function. However, the Schubert-Bornschein type of CSNB discussed in this thesis, is characterised by the signal transmission defect between photoreceptors and bipolar cells. The ERG shows this defect as the typical electronegative form, and the diagnosis is mainly based on this observation. Thus, even though “CSNB” refers to a function, CSNB is not diagnosed based on scotopic visual functions. Riemslag\(^a\) stressed that in terminology of disorders there should be a clear cut distinction between the description of visual functions and the name of a disorder. We should name disorders by their cause and/or disrupted anatomical structure. We therefore recommend to change the name CSNB into more neutral terms, for instance, “ON-bipolar deficiency” for CSNB1 and “photoreceptor synapse deficiency” for CSNB2. Because of the changes in health care that focuses more on the patient, and the recent introduction of ICF and application of the ICD and ICF structure in rehabilitation, there is now good reason to reconsider the naming of the disorder CSNB.
Chapter 7

FINAL REMARKS

The application of ICD and ICF structure in rehabilitation also demonstrates where rehabilitation falls short. The ICD recommends the determination of the exact cause of the visual impairment of the patient. This may not only include the correct diagnosis but also, in case of a genetic disorder, the genetic mutation. This information is valuable for both science and medicine. Research on retinal structure accompanies genetic research and improves our understanding of retinal function. This may lead to improved rehabilitation and possible future therapies, for instance, gene therapy. For the patient, determination of his diagnosis, including DNA analysis, provides clarity and helps to understand a person’s impaired visual functions and disabilities. Furthermore, certainty about the diagnosis and confirmation by molecular analysis is the basis for genetic counselling. The professional is able to compare patients with the same disorder, which makes it easier to inform patients on their possibilities and restrictions.

However, a diagnosis only predicts a patient’s impairments to a certain extent. As shown in the study on CSNB (Chapter 5), patients with similar genetic mutations may still show very different visual functions. This is where the ICF comes in. Because all patients are different, it remains crucial to examine every patient’s visual functions to be able to advise the patient. Therefore, we need standardized examination tests. The fact that night blindness cannot be measured adequately with today’s available tests, is against ICF recommendations. Most patients with only moderate visual impairment would like to drive a car. In The Netherlands, driving at night is legally prohibited if the dark adapted threshold is more than one log elevated compared to the threshold of healthy subjects. As far as we know, this limit is not evidence based. It is still unclear what the minimal visual functions should be, during the day or at night, to be able to drive safely. Patients want to participate in society as independently as anyone else. With this and future studies, we aim to contribute to this ambition of independency.
REFERENCES


