SPEECH, VOICE, LANGUAGE AND COGNITION IN INDIVIDUALS WITH SPINOCEREBELLAR ATAXIA (SCA)

Ellika Schalling
Dedication:
This thesis is dedicated to all the individuals who participated in the studies, for all their contributions
**ABSTRACT**

Spinocerebellar ataxias (SCA) constitute a group of genetically defined hereditary, degenerative, progressive diseases affecting the cerebellum and its connections. Few previous investigations have focused on how SCA affects different aspects of communication. The aim of the present investigation was to characterize speech and voice in individuals with SCA and to investigate the progression of speech and voice symptoms, using both perceptual and acoustic methodology. In addition, language and cognition in individuals with SCA were studied.

Thirty-two individuals with spinocerebellar degenerative disease participated in the studies. The majority had been diagnosed with SCA using molecular genetic testing and the rest were clinically diagnosed by a specialist in neurology. Matched control subjects were included in study II and III.

Speech and voice in individuals with SCA were assessed perceptually by a group of four speech-language pathologists with long experience of neurogenic communication disorders. Recorded speech samples from individuals with SCA were rated using visual analogue scales, VAS. Speech samples were also used for computer-based acoustic analysis. Speech and voice were characterized by the following perceptual parameters: equalized stress, imprecise consonants, vocal instability, monotony, strained-strangled voice, stereotypic intonation and reduced speech rate. Factor analysis resulted in two main factors; one associated with temporal aspects of speech and the other with vocal quality. Acoustic analysis confirmed the perceptual findings. Rate of speech and sequential and alternating motion rates were reduced, and duration and variability of syllables and pauses during rapid syllable repetition were increased compared to matched control subjects. Inter-stress intervals (ISIs) were also longer and more variable in subjects with SCA compared to control subjects. Perceived vocal instability was confirmed acoustically by increased coefficient of variation of fundamental frequency, CV of \( F_0 \), during sustained phonation. This was also found in individuals with SCA with otherwise close to normal speech.

Speech and voice were followed in nine individuals with SCA during three years and speech samples were analyzed both perceptually and acoustically. Perceived imprecision of consonants and stereotypic intonation had increased during the three
years. Some acoustic measures had also changed, e.g. duration of syllables in rapid syllable repetition and duration of inter-stress intervals. In addition, there was a trend towards change in several other perceptual and acoustic measures, especially measures related to temporal aspects. Changes were more substantial in individuals with early disease onset, regardless of disease duration. An increase of mean dysarthria scores was also found.

Language and cognition were assessed in 20 individuals with SCA and control subjects matched for age, gender, length of formal education and estimated cognitive level. Executive functions and attention were most severely affected, but memory and lexico-semantic knowledge were also impaired, especially in individuals with more severely impaired estimated global cognitive level of functioning. Cognitive impairment correlated with low age at disease onset and also with impairment of motor speech function, but not with disease duration.

It was concluded that dysarthria in SCA resembles previous descriptions of ataxic dysarthria, but also includes an element of strained-strangled voice. Equalized stress was more prominent and imprecision of vowels was less common compared to previous studies. Vocal instability may be an early sign of the disease. Progression of symptoms can be seen over a three-year period, especially as increased perceived imprecision of consonants and stereotypic intonation, but also measured with a clinical dysarthria test. Cognition was impaired in individuals with SCA, especially executive functions and attention. Assessment by speech-language pathologists should include testing of cognition and language as it may have implications for treatment.

Keywords: Spinocerebellar ataxia, ataxic dysarthria, perceptual analysis, acoustic analysis, cerebellar degenerative disorders, cognitive impairment, language impairment, executive dysfunction, progression of neurological disease.
Spinocerebellära ataxier (SCA) är en grupp ärftliga, degenerativa, progredierande sjukdomar som drabbar lillhjärnan och dess förbindelser. Få tidigare studier har undersökt hur SCA påverkar olika aspekter av kommunikationsförmågan. Målsättningen med denna doktorsavhandling var att beskriva tal- och röstfunktion hos personer med SCA samt att undersöka tal- och röstsymtoms progression. Vidare undersöktes hur kognitiva och språkliga förmågor påverkades av SCA.

Trettiotvå personer med SCA deltog som försökspersoner i avhandlingens fyra delstudier. De flesta av försökspersonerna hade en molekylärgenetiskt baserad SCA-diagnos, medan övriga försökspersoner hade diagnostiserats av kliniskt erfarna specialister inom neurologi. I studie II och III ingick även matchade kontrollpersoner.

grundtonen var högre hos personer med SCA jämfört med matchade kontrollpersoner. Ökad instabilitet i fonationen kunde noteras också hos individer som för övrigt hade mycket små tecken på förändringar i talet och för vilka klinisk dysartribedömning var i stort sett normal. Detta kan ses som ett objektivt mätbart tidigt sjukdomstecken.

Hos nio personer med SCA följdes tal- och röstsymtom under tre års tid. Parametrarna oprecisa konsonanter och stereotyp intonation fick högre skattade värden efter tre år. Några akustiska mått hade också ökat, t ex duration av stavelsen /ta/ vid hastig stavelseupprepning och duration av s k inter-stress intervall. Resultat från ett kliniskt dysartritest visade också en klar försämring under den aktuella tidsperioden. Förändringarna var större för individer med tidigt insjuknande i SCA jämfört med personer som insjuknat senare i livet, oavsett sjukdomslängd.

LIST OF PUBLICATIONS

The doctoral thesis is based on the following four original papers, which will be referred to in the text by their Roman numerals.

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<table>
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<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMR</td>
<td>Alternating Motion Rate</td>
</tr>
<tr>
<td>ADCA</td>
<td>Autosomal Dominant Cerebellar Ataxia</td>
</tr>
<tr>
<td>BNT</td>
<td>Boston Naming Test</td>
</tr>
<tr>
<td>CA</td>
<td>Cerebellar ataxia</td>
</tr>
<tr>
<td>CAG</td>
<td>Three nucleotides in the DNA code: Cytosine-Adenine-Guanine</td>
</tr>
<tr>
<td>CTG</td>
<td>Three nucleotides in the DNA code: Cytosine-Thymine-Guanine</td>
</tr>
<tr>
<td>DAT</td>
<td>Digital Audio Tape</td>
</tr>
<tr>
<td>DME</td>
<td>Direct Magnitude Estimation</td>
</tr>
<tr>
<td>DRPLA</td>
<td>Dentatorubral-pallidoluysian atrophy</td>
</tr>
<tr>
<td>EAIS</td>
<td>Equal-Appearing Interval Scale</td>
</tr>
<tr>
<td>F0</td>
<td>Fundamental Frequency</td>
</tr>
<tr>
<td>FDA</td>
<td>Frenchay Dysarthria Assessment</td>
</tr>
<tr>
<td>ISI</td>
<td>Inter-Stress Interval</td>
</tr>
<tr>
<td>ISW</td>
<td>Irregularly Spelled Words</td>
</tr>
<tr>
<td>MWIT</td>
<td>Multiple Word Intelligibility Test</td>
</tr>
<tr>
<td>ORD</td>
<td>Ordinal</td>
</tr>
<tr>
<td>RAVLT</td>
<td>Rey Auditory Verbal Learning Test</td>
</tr>
<tr>
<td>SCA</td>
<td>Spinocerebellar ataxia</td>
</tr>
<tr>
<td>SLDT</td>
<td>Swedish Lexical Decision Test</td>
</tr>
<tr>
<td>SMR</td>
<td>Sequential Motion Rate</td>
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<tr>
<td>TMT</td>
<td>Trail Making Test</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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<tr>
<td>WAIS-R</td>
<td>Wechsler Adult Intelligence Scale-Revised</td>
</tr>
</tbody>
</table>
1 INTRODUCTION

1.1 SPINOCEREBELLAR ATAXIA

Spinocerebellar ataxias are a group of hereditary progressive degenerative disorders affecting the cerebellum and its connections. The autosomal dominant cerebellar ataxias are characterized by a number of neurological symptoms including ataxia of gait, stance and limbs, oculomotor disturbance, retinopathy, spasticity, extrapyramidal movement disorders, peripheral neuropathy, sphincter disturbances, dysarthria, cognitive impairment and epilepsy. There is a large overlap of the phenotype between genetic subtypes and also variability of clinical symptoms within a genetic subtype of SCA. The term cerebellar ataxia is often used in the event that the phenotype closely resembles SCA but molecular identification is lacking. This may be due to the fact that some SCA genes remain to be identified (Schöls et al., 2004).

Cerebellar ataxias can also be recessively inherited; Friedreich’s ataxia being the most common and best known recessive subtype. The recessive ataxias are considered to be clinically even more heterogeneous than the dominant ataxias and may manifest as multisystem disorders (van de Warrenburg et al., 2005).

1.2 CLASSIFICATION AND DIAGNOSIS OF CEREBELLAR DEGENERATIVE DISEASE

Classification of cerebellar ataxias has been a challenge for many years. A simple classification of autosomal dominant cerebellar ataxias (ADCAs) was suggested by Harding (1982). This classification system was based on clinical characterization into four different groups: ADCA I, inherited cerebellar ataxia with extracerebellar signs; ADCA II, cerebellar ataxia with pigmentary retinal degeneration; ADCA III, “pure” cerebellar syndrome and ADCA IV, cerebellar ataxia with myoclonus and deafness. The first gene involved in inherited ataxia, spinocerebellar ataxia type 1 (SCA1), was identified in 1993 (Orr et al., 1993) and since then diagnostic classification based on molecular genetic technologies has become increasingly used. In early 2007, there were 32 known loci for dominant cerebellar ataxias. In 19 of these loci a causative gene has been identified (Bird, 2007). There are 26 known distinct genetic forms of spinocerebellar ataxia (SCA1-8, SCA 10-23, SCA25-28). Dentatorubral-pallidoluysian atrophy, DRPLA, is also commonly classified within this group of disorders (Cagnoli, 2006). There are now molecular genetic tests available for a number of the SCAs.
Diagnosis typically includes a neurological examination, neuroradiologic examination, documentation of the family history to explore a possible family history of ataxia and molecular genetic testing. Since genetically distinct forms of SCA may display differences in the clinical phenotype, a neurological examination may help in identifying clinical phenotypes characteristic of a genetic form of ataxia. Differential diagnosis must include other acquired non-hereditary causes of ataxia such as vascular disease, toxic or metabolic changes, multiple sclerosis and primary or metastatic tumours or paraneoplastic diseases. Differential diagnosis is crucial because treatments may be available.

1.3 PREVALENCE OF SCA
Estimated prevalence of SCA has been approximately 3/100 000 people (van de Warrenburg, al., 2002), although estimates as high as 8/100 000 have been suggested more recently (Craig et al., 2004). Prevalence for autosomal dominant ataxia was 3.0/100 000 in Oslo County in a recent Norwegian study (Koht and Tallaksen, 2007). There are regional differences in prevalence of individual subtypes of SCA, possibly due to founder effects (i.e. the difference between the gene pool of a population as a whole and that of a newly isolated population), SCA2 is e.g. more common among Cubans and SCA3 among people born in the Azores (Bird, 2007; Soong, 2004). It has been suggested that SCA1, SCA2, SCA3, SCA6 and SCA7 are the most common subtypes of SCA, accounting for about 70% of dominant SCA cases (Margolis, 2002).

1.4 CLINICAL FEATURES AND PATHOGENESIS OF SCA1, 2, 3, 7, 8 AND 17
In the present investigation only subjects with SCA1, SCA2, SCA3, SCA7, SCA8 and SCA17 are included and therefore the following descriptions of pathogenesis and clinical features will mainly focus on these SCA subtypes.

Maschke et al. (2005) studied clinical feature profiles in SCA type 1-8 and reported that age at onset of disease was around 30 +/- approximately 10 years for SCA1, SCA2, SCA3, SCA5 and SCA7. SCA6 has a significantly higher age at onset, close to age 50 +/- approximately 10 years, and SCA4 and SCA8 had a mean age at onset intermediate between SCA6 and the other subtypes. Marked variability in the age of onset, ranging from 18 to 55 years has been reported in SCA17 (van de Warrenburg et al., 2005).
SCA1, SCA2, SCA3, SCA6, SCA7, SCA17 and dentatorubral-pallidoluysian atrophy (DRPLA) are caused by CAG trinucleotide repeat expansions within the coding sequences of their respective genes (see table 1). The molecular diagnosis for these disorders is based on mutation analysis of the CAG trinucleotide repeat length. For some disorders there is however an overlap between the upper range of normal and the lower range of abnormal CAG repeat size and there may be a “gray zone” in which it is not clear if the allele is associated with phenotypic abnormalities or not. This is particularly problematic in pre-symptomatic testing. SCA8 is associated with a CTG expansion. Anticipation is observed in ataxias caused by CAG repeats. Anticipation means a younger age of onset and more severe disease course in subsequently affected generations. Among the SCAs, anticipation is thought to be explained by an expansion of repeat length in transmission to the subsequent generation (Margolis, 2003). Cancel et al. (1997) showed a strong negative correlation (r=-0.81) between age at onset and CAG repeat numbers in SCA2 and similar results have been shown in several other subtypes of SCA (Dürr et al., 1998; Johansson et al., 1998; Stevanin et al., 2000). CAG codes for glutamine and these disorders have also been called polyglutamine disorders. The expansion of the CAG-repeat sequence leads to abnormally long polyglutamine tracts in the encoded proteins, resulting in a toxic process with aggregation and deposition of misfolded proteins leading to neuronal dysfunction and eventually cell death (Koeppen, 2005; Dueñas et al., 2006). In SCA8, there is a CTG repeat expansion outside the coding region of the disease gene leading to dysregulation of gene expression. There is overlap in clinical phenotype between different subtypes of SCA and diagnosis can seldom be based only on clinical features. There are however some distinguishing clinical features (see table 1).
<table>
<thead>
<tr>
<th>Disease</th>
<th>Gene</th>
<th>Locus</th>
<th>Gene product</th>
<th>Repeat type/normal number</th>
<th>Abnormal repeat number</th>
<th>Age of onset</th>
<th>Distinguishing features (gait and limb ataxia present in all)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>ATXN1</td>
<td>6p23</td>
<td>Ataxin-1</td>
<td>CAG/6-44</td>
<td>39-91</td>
<td>4th decade (10-60)</td>
<td>Pyramidal signs, peripheral neuropathy</td>
</tr>
<tr>
<td>SCA2</td>
<td>ATXN2</td>
<td>12q24</td>
<td>Ataxin-2</td>
<td>CAG/&lt;30</td>
<td>&gt;32;33</td>
<td>3rd -4th decade (10-60)</td>
<td>Slow saccadic eye movement, peripheral neuropathy, cognitive impairment</td>
</tr>
<tr>
<td>SCA3</td>
<td>ATXN3</td>
<td>14q24.3-q31</td>
<td>Machado-Joseph disease protein 1</td>
<td>CAG/&lt;47</td>
<td>53-86</td>
<td>4th decade (10-70)</td>
<td>Pyramidal and extrapyramidal signs; lid retraction, nystagmus, decreased saccade velocity, amyotrophy fasciculations, sensory loss</td>
</tr>
<tr>
<td>SCA7</td>
<td>ATXN-7</td>
<td>3p21.1-p12</td>
<td>Ataxin-7</td>
<td>CAG/4-35</td>
<td>&gt;36-450</td>
<td>3rd-4th decade (0.5-60)</td>
<td>Visual loss with retinopathy, pyramidal signs</td>
</tr>
<tr>
<td>SCA8</td>
<td>KLHL1AS</td>
<td>13q21</td>
<td>-</td>
<td>CTG/15-50</td>
<td>(71)80-800</td>
<td>39 (18-65)</td>
<td>Brisk reflexes and decreased vibration sense</td>
</tr>
<tr>
<td>SCA17</td>
<td>TBP</td>
<td>6q27</td>
<td>TATA-box binding protein</td>
<td>CAG/25-44</td>
<td>45-63</td>
<td>3rd decade (6-48)</td>
<td>Cognitive impairment, psychiatric symptoms, later pyramidal and extrapyramidal signs (parkinsonism, chorea or dystonia)slow saccades, epilepsy</td>
</tr>
</tbody>
</table>
1.5 THE STRUCTURE AND FUNCTION OF THE CEREBELLUM

The cerebellum is located dorsal to the brainstem in the posterior fossa, inferior to the tentorium cerebelli. It is connected to the pons, medulla and mesencephalon through three peduncles on each side. The cerebellum constitutes about 10-15% of the entire brain weight, but it contains about half of the brain’s neurons. It has two hemispheres, a highly convoluted cortex and a core of white matter with three nuclei embedded on each side, see figure 1.

Illustrations by Per Östberg

Figure 1. The cerebellum, lateral view and sagital section.

The cerebellum is part of feedforward and feedback motor loops. The feedforward loop projects from the cerebral cortex, to pontine nuclei and then to the dentate nucleus of the cerebellum. The feedback loop projects from the dentate nucleus, to the thalamus and back to the cerebral cortex. These feedforward and feedback loops are thought to be critical in the sequencing of complex movements and in the fine adjustment of the forces needed by different muscles in order to perform smooth sequences of movements. The cerebellum receives input on intended movements from the cerebral cortex and monitors the produced movements based on feedback from muscles, tendons and joints. In cerebellar disease the main motor symptom is incoordination of movement. The term ataxia refers to the incoordinated but purposeful movements in patients with cerebellar disease. Dysmetria is another term associated with ataxia. It refers to the difficulties with scaling and timing of movements. E.g when reaching for an object the patient may overshoot and miss the target. Repetitive movements tend to be produced in an irregular fashion. When the smooth sequencing and scaling of movements is impaired, it can give the impression that complex movements are broken
down into single components performed one after the other, sometimes referred to as decomposition of movement. Other motor symptoms associated with cerebellar disease are reduced muscle tone or weakness. Postural instability and oculomotor dysfunction, e.g. nystagmus or ocular dysmetria are also common (Cannito and Marquardt, 1997; Duffy, 2005; Weismer, 2007). Common complaints from patients with cerebellar disease are loss of balance, slurred speech and loss of automaticity of movements. The loss of automaticity of movement, both in e.g. gait, but also in speech movements, was described by several of the individuals with SCA who participated in the present investigation. The problem was expressed by one of them with the following words: “When I walk I have to think about every step I take, and when I speak I have to think about how I pronounce the words. It is impossible to walk and speak at the same time”.

Attempts have been made to localize speech within the cerebellum, both in neuroimaging studies of healthy speakers and in studies of lesions resulting in ataxic dysarthria. No definite conclusions have been reached yet, but in many studies there is an association between overt speech and bilateral activation of the cerebellar hemispheres, especially for more complex speech tasks. It has been suggested that motor speech execution is correlated with bilateral hemispheric activation, whereas motor speech planning and processing may be more lateralized to the right cerebellar hemisphere (Spencer and Slocomb, 2007; Kent et al., 2001). Ackerman et al. (1992) also discussed that phonatory disturbances may be linked to lesions of the dentate nucleus.

Traditionally, the cerebellum has been considered to be involved only in motor coordination, but in the last decade or so there has also been an increasing interest in the role of the cerebellum in cognitive processing, including language. Examples of findings from recent years are cases with agrammatism following cerebellar stroke (Silveri et al., 1994; Zettin et al., 1997), reduced verbal fluency (Appollonio et al., 1993; Bürk et al., 1999; Leggio et al., 2000), reduced verbal memory (Silveri et al., 1998; Ravizza et al., 2006) and executive dysfunction (Schmahmann and Sherman, 1998; Vokaer et al., 2002). It has been suggested that these and similar findings are not direct evidence that the cerebellum per se is involved in cognitive and linguistic processing, but that cognitive and linguistic dysfunction in cerebellar patients may be related to interruptions of cerebro-ponto-cerebello-thalamico-cerebral-loops. For an overview see Paquier and Mariën (2005).
1.6 DYSARTHRIA CLASSIFICATION
In the first decades of the 1900 century it was recognized that dysarthria was a speech deficit different from aphasia, e.g. by Head (1926). As early as in 1877, Charcot gave a description of what he considered highly characteristic of disseminated sclerosis including the following key features; slow and sometimes unintelligible speech, an impression that the tongue of the patient is “too thick” and speech resembling the speech of an intoxicated person. He also described that the words were measured or scanned with a pause after every syllable, that the syllables themselves were pronounced slowly and the speech was hesitant. In addition, poor pronunciation of certain consonants such as “l”, “p” and “g” were mentioned (Charcot, 1877). His description is very similar to characterizations of dysarthria associated with cerebellar disease in more recent years. Another early description of speech problems associated with the cerebellum was done by Zentay (1937), who used the term “ataxic” in reference to speech problems associated with cerebellar damage. He concluded that the motor incoordination could affect both articulation, respiration and phonation and result in slow, explosive-hesitant and scanning speech. In the middle of the last century Grewel (1957) recognized that different types of dysarthria may reflect different neuroanatomical or neurophysiological deficits and he suggested that differential diagnosis of the dysarthrias may even be helpful in tentative diagnosis of neurological disease. He proposed a classification system including 14 types of dysarthria based on neuroanatomical site and etiology.

1.7 PERCEPTUAL ANALYSIS OF DYSARTHRIC SPEECH
The idea that auditory-perceptual features of the various dysarthrias are functions of localization of neurological impairment was discussed in the middle of the last century, but won broad acceptance through the work by Darley, Aronson and Brown (1969a). They introduced a system for classification of the dysarthrias, based on perceptual features, including articulatory, respiratory, phonatory, resonance and prosodic disorders in relation to neuroanatomical lesion that is still widely recognized as a framework for both clinical work and research. Their work was based on a study of 212 patients with dysarthria secondary to different neurological disorders. Darley et al. identified 38 different deviant dimensions of speech for perceptual ratings. Ratings were done on a 7-point scale with “1” representing normal speech and “7” representing severe deviation from normal. Statistical analysis of data from the 212 patients resulted
in descriptions of what speech dimensions were characteristic of each of the neurological disorders included in the study. Other protocols of lesser detail, or protocols including other speech dimensions have been developed later, but similar principles are usually followed in perceptual analysis of disordered speech.

1.7.1 Reliability of perceptual analysis

Perceptual analysis is probably the most common tool used in assessment and classification of disordered speech. Perceptual assessment of vocal function is e.g. widely used in clinical work (Hammarberg, 2000). The advantage is of course the availability; no expensive equipment is needed and analysis may be done in real-time, even without recording of a speech sample. There has been critique however, mainly concerning the lack of common definitions of perceptual dimensions and reliability. Other issues that have been discussed include probable interdependence between different perceptual dimensions and the relevance of specific dimensions for particular disorders (Kent, 1996).

The reliability of perceptual analysis in identification of different dysarthria types was questioned by Zyski and Weisiger (1987) in a study where three different listener groups were asked to derive the dysarthria type or neurological disease based on perceptual speech dimensions. None of the groups (experienced speech pathologists or speech-language pathology graduate students who received five hours of classroom training in perceptual analysis) were sufficiently successful in identifying the dysarthria type according to the authors. The question of reliability was also raised by Zeplin and Kent (1996) who replicated the work by Darley et al. (1969a). They obtained the original recordings used by Darley et al. and rated the speech samples again, using the same methodology. Their results were only moderately in agreement with the results of the ratings by the original authors. Of the ten highest ranked speech dimensions in each study, only four speech dimensions were ranked among the top ten in both studies (monoloudness, monopitch, imprecise consonants and excess and equal stress). Differences in reliability of judgments between different speech dimensions were investigated by Sheard et al. (1991) in a study of ratings of five speech dimensions (imprecise consonants, excess and equal stress, irregular articulatory breakdown, distorted vowels and harsh voice) by 15 experienced speech pathologists. It was found that agreement between judges varied between different dimensions. The lowest agreement was obtained for irregular articulatory breakdown and harsh voice. The
authors discussed inter-correlations between dimensions and the difficulties associated with rating one dimension without being influenced by other dimensions. There was little relationship between speaker’s intelligibility scores and inter-judge agreement for any of the speech dimensions in the study. Other studies, e.g. perceptual studies of voice quality have however reported high reliability granted that there is consensus on definitions of terminology (Hammarberg, 1986).

Measures to be taken in order to optimize validity and reliability of perceptual analysis include making sure there is consensus on definitions of the speech dimensions to be used, also training of the judges including training with reference samples (Kreiman et al., 1993; Kent, 1996).

1.7.2 Rating scales in perceptual analysis

The equal-appearing interval scale, EAIS, which was used in the work by Darley et al. (1969a), is the most prevalent in perceptual analysis. Seven-point scales are most commonly used, followed by five-point scales. Agreement within and between judges is often reported plus or minus one scale value (Kreiman et al., 1993). A few disadvantages with the EAIS have been suggested; e.g. that the number of intervals may be too small to give the expert listener the possibility to make subtle discriminations and that there is no evidence to suggest that speech and voice features are perceived in equal magnitude steps, which may lead to loss of important information. Listeners also tend to avoid scale extremes, which in practice further reduces the scale. Reporting agreement with plus or minus one scale value e.g. on a five-point scale where listeners may avoid scale extremes may in reality mean that chance level of agreement is unacceptably high in EAIS (Kreiman et al., 1993).

Direct magnitude estimation (DME) is another type of scaling technique which has been used in perceptual analysis. DME is a scale where a given speech dimension is judged compared to a base-line sample, the listener may e.g. judge if a speech dimension is half, twice or three times different from the base-line. Listener reliability and cross-study comparisons have been a concern in DMEs, but they may be especially suited for ratings of nasality and intelligibility (Tjaden, 2007).

Another scale that has been used in perceptual analysis is the Visual Analogue Scale (VAS), which typically is a 100 mm graphic scale where ratings are made by marking
anywhere along the line. High interrater-reliability has been reported in studies using VAS where there was consensus on definitions on terminology, e.g. by Sederholm et al. (1993), McAllister et al. (1994) and by Södersten and Hammarberg (1993).

The different qualities in the VAS and EAIS have been debated. Yiu and Ng (2004) compared an 11-point EAIS with a 100 mm VAS in a study of perceptual assessment of breathy- and rough voice quality. They found that intra-rater agreement was higher and inter-rater variability was lower using the EAIS, however there was a bias in using certain points on the EAIS in contrast to the VAS. Their conclusion was however that the EAIS was preferable due to ease of use, but not necessarily superior. Yu et al (2002) compared perceptual ratings using a VAS and a 4-point ordinal (ORD) scale and found that correlations between perceptual and objective measures were better using a VAS than an ORD-scale. In the present investigation all perceptual rating were made using VAS based on the arguments presented above.

1.8 ACOUSTIC ANALYSIS OF DYSARTHRIC SPEECH

Acoustic analyses offer objectively quantifiable ways of characterizing disordered speech. Temporal characteristics may be examined through measurement of duration of different segments of the speech signal. Spectral characteristics may also be explored and phonatory characteristics can be investigated by studying e.g. fundamental frequency, F0, or period-to-period variability in pitch and amplitude (jitter and shimmer) as well as long-term phonatory instability (Kent et al., 1999).

Several studies have focused on defining speech tasks most sensitive to diagnose or describe different types of dysarthria. Kent et al. (2000) studied 14 individuals with ataxic dysarthria, using both perceptual and acoustic analysis and found deviations in most of the speech tasks they studied, including alternating and sequential motion rates (AMR/SMR), speech rate in sentence recitation and conversation and sustained phonation. Also in other studies focusing on task profiles it has been found that sustained phonation, syllable repetition and conversational speech are tasks especially useful in characterizing ataxic dysarthria as they may reveal F0 and amplitude variability, slow and irregular syllable production and a “scanning” speech pattern in continuous speech (Kent et al., 1997; Kent and Kent, 2000).
1.9 ATAXIC DYSARTHRIA

1.9.1 Perceptual speech dimensions in ataxic dysarthria

A specific perceptual description of ataxic dysarthria based on data from 30 patients included in the study by Darley et al. (1969a) was published the following year (Brown et al., 1970). The 10 most prominent deviant speech dimensions that comprised the ataxic dysarthria in the 30 patients with cerebellar lesions are shown in table 2.

Table 2. Perceptual speech dimensions in ataxic dysarthria

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Mean scale value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imprecise consonants</td>
<td>3.19</td>
</tr>
<tr>
<td>Excess and equal stress</td>
<td>2.69</td>
</tr>
<tr>
<td>Irregular articulatory breakdown</td>
<td>2.59</td>
</tr>
<tr>
<td>Vowels distorted</td>
<td>2.14</td>
</tr>
<tr>
<td>Harsh voice</td>
<td>2.10</td>
</tr>
<tr>
<td>Phonemes prolonged</td>
<td>1.93</td>
</tr>
<tr>
<td>Intervals prolonged</td>
<td>1.76</td>
</tr>
<tr>
<td>Monopitch</td>
<td>1.74</td>
</tr>
<tr>
<td>Monoloudness</td>
<td>1.62</td>
</tr>
<tr>
<td>Slow rate of speech</td>
<td>1.59</td>
</tr>
</tbody>
</table>

(From Brown, Darley, Aronson, 1970)

The speech dimension "imprecise consonants" was common, but it is prominent in most types of dysarthria and therefore of little diagnostic value. "Irregular articulatory breakdowns" (sudden, inconsistent telescoping of one or several syllables) is prominent in both severity and frequency and very suggestive of ataxic dysarthria. The speech dimension “excess and equal stress” (excess vocal emphasis placed on usually unstressed syllables and words) was also both frequent and prominent. A few dimensions were more dependent on severity of the ataxia, e.g. “vowels distorted”, “harsh voice”, “phonemes prolonged” and “monotony”, which were frequently absent in cases of mild impairment.

Darley et al. (1969b) also divided the 10 most deviant speech dimension into three clusters; articulatory inaccuracy (irregular articulatory breakdown, imprecise
consonants, distorted vowels), prosodic excess (excess and equal stress, prolonged phonemes, prolonged intervals, slow rate) and phonatory-prosodic insufficiency (monoloudness, monopitch, harsh voice). Speech dimensions from all three clusters were present in ataxic dysarthria.

1.9.2 Articulation, speech rate and rhythm in ataxic dysarthria

Reduced speech rate both for syllable repetition, word production and continuous speech has been found in ataxic dysarthria (Ackermann & Hertrich, 1994; Kent et al., 2000). A reduction of sequential motion rates (SMRs) and alternating motion rates (AMRs) in ataxic dysarthria has been reported in several studies (Portnoy and Aronson, 1982; Ackermann et al, 1995; Kent et al., 1997; Ziegler, 2002). Ziegler and Wessel (1996) reported the somewhat contradictory finding that ataxic subjects even had longer syllable durations in rapid syllable repetition tasks than in sentence production tasks requiring similar articulations. The diadochokinetic speech performance in ataxic dysarthria was also studied by Boutsen et al. (1997) who emphasized the importance of variability measures of rate and intensity and suggested that they may offer a way to subgroup individuals into different types of ataxic dysarthria. Reduced SMR/AMRs as well as increased variability of syllable durations in SMR/AMR have also been reported in subjects with Friedreich’s ataxia (Gentil, 1990).

Lengthening of segments and alterations in speech rhythm in ataxic dysarthria were described already by Kent et al. (1979). They studied timing patterns and noted prolongations of speech segments and a tendency towards equalized syllable durations. They also noted that subjects with ataxic dysarthria made smaller reductions of syllable durations in words when suffixes were added (and word length increased) compared to normal control subjects. Also, Ackermann and Hertrich (1994) found reduced intra-utterance variability as well as increased inter-utterance variability of syllable durations in subjects with cerebellar disease. Hartelius et al. (2000) made similar findings in their investigations of subjects with ataxic dysarthria secondary to multiple sclerosis. They studied both the timing and variability of syllables, and also the timing of larger rhythmic units, often referred to as stress groups. Both Swedish and English are referred to as stressed-timed languages, versus e g French which is referred to as syllable-timed. Normally, in stress-timed languages, the stress (the “rhythmic beats” in continuous speech) falls regularly with equal time intervals. These intervals can be measured as inter-stress intervals, ISIs, each interval beginning with the onset of the
vowel in the stressed syllable. In normal speech these time intervals are expected to be
isochronous (“at equal time”). They found that the dysarthric group had significantly
increased durations of inter-stress intervals and also significantly increased duration
variability compared to the control group in addition to increased duration but a
tendency towards decreased variability for syllables.

Imprecision of consonants and distortion of vowels are salient perceptual features in
ataxic dysarthria and have been associated with impaired control of range, velocity,
force and timing of movements of the lips, tongue and jaw (Kent et al. 1979).
Spectographic studies have shown lengthened formant transition and frictionalization
of stop gaps, in addition to the rate alterations and lengthening of vowel and formant
segments. Articulatory positions and movements were studied in ataxic speakers using
cineradiography by Kent and Netsell (1975) and Netsell and Kent (1976). They
identified abnormal articulatory movements, such as small adjustments of anterior-
posterior tongue movements during vowel production and this was suggested to be
related to the perceptual feature of distorted vowels.

1.9.3 Phonation in ataxic dysarthria
In the perceptual analysis by Brown et al. (1970), “harshness” and “monotony of pitch”
were the two dimensions related to phonation that were rated among the ten most
salient dimensions. Phonation has been studied with acoustic methodology in several
studies on ataxic dysarthria. Both short-term measures (cycle-to-cycle variations in
frequency and amplitude, i.e. jitter and shimmer) and long-term measures of phonatory
instability have been found. Kent et al. (2000) reported increased measures for jitter in
women and for shimmer in both men and women with ataxic dysarthria compared to
normal controls. Measures of jitter and shimmer correspond to the perceptual feature
“harsh voice quality”, whereas the long-term measures reflect slower, cyclic variations
in frequency and intensity corresponding to perceptual impressions of vocal instability
or voice tremor. Kent et al. (2000) also reported long-term phonatory irregularities in
speakers with ataxic dysarthria compared to normal controls. Ackermann and Ziegler
(1991) reported rhythmic oscillations at a rate of about 3 Hz during sustained phonation
in a case study of a woman with a purely cerebellar syndrome. Zwirner et al. (1991)
found increased measures of jitter and shimmer in several groups of neurologically
impaired patients including patients with cerebellar ataxia, but also significantly higher
values for standard deviation of fundamental frequency (reflecting long-term phonatory
instability) in subjects with cerebellar ataxia. Ackermann and Ziegler (1994) also reported increased measures of jitter as well as increased pitch fluctuations during sustained phonation.

Hertrich et al. (1997) investigated gender differences in phonatory dysfunctions in subjects with neurological disorders of the basal ganglia and the cerebellum, including Friedreich’s ataxia and cerebellar atrophy, using both perceptual and acoustic methodology. Perceptual analysis was done by five speech pathologists who rated vocal quality in sustained vowels with respect to the dimensions “breathy”, “harsh”, “strained”, “creaky”, “quiver”, “pitch fluctuations” and “loudness fluctuations” on a four point scale. In female subjects with cerebellar atrophy “strained” was the dimension with the highest rating, but all dimensions except “creaky” had significantly higher ratings than in the control group. In male subjects with cerebellar atrophy only “harsh” was significantly higher than in the control group, although “breathy” was the dimension with the highest mean rating. The acoustic analysis showed that several of the acoustic measures reached statistical significance in female subjects with neurological disease, compared to female control subjects; long-term instability score (“pitch” and “loudness fluctuations”, “quiver” “F0 variation coefficient” and “variation coefficient of F0 period amplitudes”) were particularly high. In the male group only “variation coefficient of F0 period amplitudes” was significantly different compared to male control subjects.

1.9.4 Resonance and respiration in ataxic dysarthria

Velopharyngeal dysfunction is not a commonly reported finding in ataxic dysarthria. No speech dimensions related to nasality were among the ten most salient dimensions in the perceptual analysis by Brown et al. (1970). Hypo-nasality is however sometimes observed in speakers with cerebellar disease and intermittent hypo-nasality may also be encountered. According to Duffy (2005) this may reflect difficulties with timing of velar and articulatory gestures for nasal consonants.

Individuals with cerebellar disease often clinically give the impression to have difficulties with speech breathing; they may seem to easily be out of breath, to speak in short phrases and to make pauses to inhale in the middle of sentences. It was found already by Brown et al. (1970) that some of their subjects with ataxic dysarthria had reduced vital capacity and demonstrated limited ability to sustain /a/. This led the
authors to suggest a breakdown in the timing of onset of respiration and phonation in these speakers. Murdoch et al. (1991) studied 12 subjects with cerebellar disease using spirometric and kinematic techniques. They also found reduced vital capacities (in almost one-half of the subjects) and a tendency to initiate utterances at lower than normal lung volume levels. Unusual patterns of chest wall two-part contribution to lung volume change, abdominal and rib cage paradoxing and abrupt changes in movements of the rib cage were also found. The authors felt that these findings reflected poor coordination of the chest wall and that it was possible that some of these respiratory anomalies were an underlying cause of some of the prosodic abnormalities observed in individuals with cerebellar disease.

1.10 DYSARTHRIA IN SPINOCEREBELLAR ATAXIA
Dysarthria is mentioned in most clinical descriptions of the SCAs, but detailed characterization of the dysarthria in individuals with SCA has not previously been done. There are no studies of phenotype compared to genotype in relation to speech and voice, i.e., studies of possible difference in symptom profiles between different subtypes of SCA. Based on what is known about neuropathological changes in SCA it can be expected that individuals with SCA will have an ataxic dysarthria, possibly also with elements of spastic or hypokinetic dysarthria due to involvement of the brainstem and spinal cord, but this has previously not been investigated in any detail.

1.11 LANGUAGE AND COGNITION IN SPINOCEREBELLAR ATAXIA
In recent years cognitive and linguistic changes in SCA have been studied by several authors. A number of studies are summarized in Table 3. Findings have varied somewhat, but include executive dysfunction and impaired attention as well as compromised verbal fluency and different kinds of memory deficits. Executive dysfunction and impaired attention seem to be the most common finding. Executive functions involve e.g., planning, organization and problem solving. Tasks assessing attention often involve both sustaining attention and being able to shift attention e.g., between two kinds of stimuli. Executive functions and attention are also sometimes referred to as frontal lobe functions, as they are known to involve processing in the frontal lobes.
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Cognition/Language</th>
<th>Other</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>Executive dysfunction</td>
<td></td>
<td>Bürk et al., 2001</td>
</tr>
<tr>
<td></td>
<td>Impaired verbal memory</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(visuospatial memory intact)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Executive dysfunction, mild deficits in verbal memory</td>
<td></td>
<td>Bürk et al., 2003</td>
</tr>
<tr>
<td>SCA2</td>
<td>Executive dysfunction</td>
<td></td>
<td>Storey et al., 1999; Bürk et al., 1999; Gambardella et al., 1998</td>
</tr>
<tr>
<td></td>
<td>Executive dysfunction and impaired attention and verbal memory</td>
<td></td>
<td>Le Pira et al., 2002</td>
</tr>
<tr>
<td></td>
<td>Executive dysfunction, mild deficits in verbal memory, impaired word finding and ability to switch semantic category</td>
<td></td>
<td>Bürk et al., 2003</td>
</tr>
<tr>
<td>SCA3</td>
<td>Slowing of visual processing, inability to shift attention, learning difficulties</td>
<td></td>
<td>Maruff et al., 1996</td>
</tr>
<tr>
<td></td>
<td>Impaired verbal attention and executive dysfunction (un-timed attention intact), reduced verbal fluency.</td>
<td></td>
<td>Zawacki, 2002</td>
</tr>
<tr>
<td></td>
<td>Mild deficits in verbal memory</td>
<td></td>
<td>Bürk et al., 2003</td>
</tr>
<tr>
<td></td>
<td>Visuospatial construction and verbal fluency impaired. Verbal visual memory deficits</td>
<td></td>
<td>Kawai et al., 2004</td>
</tr>
<tr>
<td>SCA7</td>
<td>No studies on cognition and language found</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA8</td>
<td>Attention, information processing and reasoning impaired</td>
<td></td>
<td>Lilja et al., 2005</td>
</tr>
<tr>
<td></td>
<td>Executive dysfunction, visuospatial impairment and visual memory deficits, reduced verbal fluency</td>
<td></td>
<td>Stone et al., 2001</td>
</tr>
<tr>
<td>SCA17</td>
<td>Executive dysfunction, visuoperceptual and visuospatial dysfunction, impaired memory, impaired spelling</td>
<td></td>
<td>Loy et al., 2005</td>
</tr>
<tr>
<td></td>
<td>Cognitive impairment including memory and attention</td>
<td></td>
<td>Craig et al., 2005</td>
</tr>
</tbody>
</table>
1.12 AIMS

The aim of the present study was to investigate symptoms related to different aspects of communicative functions in individuals with spinocerebellar ataxia. Specific aims were:

1) To describe characteristics of speech and voice based on perceptual analysis in a group of individuals with SCA.

2) To describe characteristics of speech and voice based on acoustic analysis in a group of individuals with SCA.

3) To investigate cognition and language in a group of individuals with SCA and also investigate the relationship between symptoms in this area with speech motor symptoms.

4) To describe progression of symptoms of speech and voice dysfunction in a group of individuals with SCA.
2 METHODS

2.1 SUBJECTS

In total, 32 subjects with cerebellar degenerative disease participated in this investigation. Twenty-three of the subjects were Swedish and they were invited to participate via their physician at the departments of neurology or clinical genetics at the university hospitals where they were treated. Nine American subjects were also included in study II and they were recruited from a university hospital in the US via the neurologist in charge of their care. Several of the subjects were studied in more than one of the papers in the thesis, see table 4. Six different subtypes of SCA were identified among the subjects in the thesis; SCA1, SCA2, SCA3, SCA7, SCA8 and SCA17. Ten subjects were also included who did not have a genetically verified SCA-diagnosis. They were however diagnosed with spinocerebellar ataxia or cerebellar ataxia by a specialist in neurology based on clinical examination and neuroradiologic examination. These subjects either had not had the opportunity to be offered molecular genetic testing or they had been tested but with a negative test result, possibly because some subtypes of SCA could not be identified by the commercially available tests at that time.

Table 4. Number of subjects with different subtypes of SCA participating in the different studies in this investigation (CA=cerebellar ataxia)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
<th>Study IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>SCA2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>SCA3</td>
<td></td>
<td>6</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>SCA7</td>
<td>2</td>
<td>3</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>SCA8</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCA17</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>9</td>
<td>4</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3</td>
<td>21</td>
<td>20</td>
<td>9</td>
</tr>
</tbody>
</table>

The age of the subjects ranged from 19 to 85 and age at onset of disease ranged from 12 to 68 years. Severity of motor symptoms also varied considerably from only slightly unsteady gait and mildly reduced fine-motor control to being wheelchair-bound with severe loss of fine-motor control. Common complaints from the subjects were
problems with balance and reduced mobility, but also slurred speech and increasing difficulties with communication.

Control subjects, individually matched for gender and age +/- 3 years were recruited for study II. For study III a new group of control subjects were recruited who were individually matched for gender, age, length of formal education and estimated level of cognitive functioning. All control subjects were native speakers of Swedish and had no history of neurological or psychiatric disease.

2.2 DYSARTHRIA ASSESSMENT

All Swedish subjects in the investigation were assessed with a Swedish standardized dysarthria assessment (Hartelius and Svensson, 1990). The test assesses different functions related to speech: Respiration, phonation, oral-motor skills, articulation, prosody and intelligibility. Each task is rated on a five-point scale from 0-4 (0=normal or insignificantly deviating function, 4=severe deviation or no function). An overall test score (mean test score) is also computed to indicate severity of impairment (ranging from 0-4, see above). Intelligibility was also tested as a part of the dysarthria assessment. It was assessed using a computerized intelligibility test version (Lillvik et al., 1999) in which randomized lists of words and sentences are generated and the percentage of correctly perceived words and sentences are calculated. For the American subjects in study II the Frenchay Dysarthria Assessment (FDA) was used (Enderby, 1983). The Swedish dysarthria test and the FDA include similar test items and could therefore easily be combined. Testscores from the FDA were converted to the same scale as used in the Swedish dysarthria test and test items were restructured into comparable categories and thus test scores for each function, as well as an overall test score could be computed in the same manner as in the Swedish test (for a detailed description see study II). Intelligibility was assessed in the American subjects with the Multiple Word Intelligibility Test, MWIT, (Kent et al., 1989). In the MWIT test results are represented as a percentage of intelligible words.

2.3 SPEECH SAMPLES AND RECORDING PROCEDURES

Speech samples included syllable repetition, sustained phonation of vowel and sustained fricative, reading of sentences and a paragraph, re-iteration of paragraph as well as spontaneous conversation, see table 5 for details about different speech tasks and type of analysis and measures derived.
Table 5. Speech tasks, types of analysis and measures, studies I-IV

<table>
<thead>
<tr>
<th>Speech task</th>
<th>Type of analysis</th>
<th>Measure</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading paragraph</td>
<td>Acoustic</td>
<td>Rate of speech, Pause duration, Number of pauses, Proportion speech/pause time, Mean fundamental frequency, F0, VAS ratings of speech parameters</td>
<td>I, II, III, IV</td>
</tr>
<tr>
<td></td>
<td>Perceptual</td>
<td></td>
<td>I</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>I and II</td>
</tr>
<tr>
<td>Re-iteration paragraph</td>
<td>Acoustic</td>
<td>Rate of speech, Pause duration, Number of pauses, Proportion speech/pause time, Mean fundamental frequency, F0</td>
<td>I</td>
</tr>
<tr>
<td>Spontaneous speech</td>
<td>Acoustic</td>
<td>Rate of speech, Pause duration, Number of pauses, Proportion speech/pause time, Mean fundamental frequency, F0</td>
<td>I</td>
</tr>
<tr>
<td></td>
<td>Perceptual</td>
<td></td>
<td>II</td>
</tr>
<tr>
<td>Syllable repetition</td>
<td>Acoustic</td>
<td>Sequential and alternating motion rates, SMR/AMR, (syll/sec) Syllable and pause durations</td>
<td>I, II, III, IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>I, II, IV</td>
</tr>
<tr>
<td>Sustained phonation</td>
<td>Acoustic</td>
<td>Fundamental frequency, F0, mean and coefficient of variation</td>
<td>I, II, IV</td>
</tr>
<tr>
<td>Sustained vowel and sustained fricative</td>
<td>Acoustic</td>
<td>Duration (milliseconds)</td>
<td>IV</td>
</tr>
<tr>
<td>Reading sentences (with even stress beats)</td>
<td>Acoustic</td>
<td>Duration and variability of inter-stress intervals (ISIs)</td>
<td>I, IV</td>
</tr>
</tbody>
</table>
Recordings of the speech material of subjects with SCA and control subjects were made in a sound-treated booth, using a Sony Digital Audio Tape Deck DTC-ZE700. An electret-condenser microphone was used. The microphone was positioned on a stick, mounted on a headset to ensure that a mouth to microphone distance of 15 cm was constantly maintained. American subjects included in study II were recorded digitally in the US using the Soundswell Software with a laptop computer (HP omnibook 6 000) and a neck collar, air-borne microphone (Labtec, LVA7370). Eleven of the recordings of subjects with SCA with reduced mobility in study III and IV were made using a portable DAT-recorder with an electret-condenser tie-pin microphone. The speech recordings were transferred to a computer for acoustic analyses using the Soundswell software (Ternström, 2000). The analogue voice signal was digitized with Sound Blaster PCI 128 at a sampling rate of 16 000 Hz. All acoustic measurements were made using this software.

2.4 PERCEPTUAL ANALYSIS
Perceptual analysis of speech and voice in study II and IV were performed using the following methodology: In study II, the first step was to develop a relevant protocol of perceptual speech and voice parameters. A group of four speech-language pathologists with extensive experience in neurogenic communication disorders first listened to speech samples from the 21 subjects with SCA included in study II and determined what perceptual parameters were salient to characterize these speech samples. Protocols from other investigations were reviewed in order to select relevant parameters (Chenery, 1998; Hammarberg, 2000; Sundberg, 2001). Definitions of terminology were discussed and clarified and a protocol including 20 perceptual speech and voice parameters was produced. The protocol was then tested by three other speech-language pathologists, who used it to rate speech samples from other individuals with speech impairment due to cerebellar disease and a few additional revisions were made following these test ratings, see table 6.
Table 6. Speech and voice parameters included in the protocol for perceptual analysis of subjects with SCA and control subjects.

**Overall impression**
1. Degree of deviation

**Phonation:**
2. Harshness
3. Glottal fry
4. Vocal instability
5. Breathiness
6. Strain-strangled
7. Vocal tremor
8. Pitch

**Articulation and prosody**
9. Imprecise consonants
10. Imprecise vowels
11. Equalized stress
12. Short phrases
13. Inappropriate silences
14. Prolonged intervals
15. Monotony
16. Stereotypic intonation pattern
17. Excessive variation of pitch
18. Speech rate
19. Mixed nasality
20. Nasal quality

A visual analogue scale (VAS) was used for all perceptual ratings. The first item was a general rating of overall impression of speech impairment with endpoints on the 100 mm VAS labeled “normal” and “very deviating”. Sixteen of the speech parameters were rated on a 100 mm VAS with endpoints representing “not present” and “present to high degree”. The parameters “speech rate” and “pitch” were rated on a 200 mm VAS with endpoints labeled “very low” and “very high” and the middle of the line labeled “normal”, since values both below and above “normal” could be expected. The parameter “nasality” was also rated on a 200 mm VAS with endpoints labeled “closed” and “open” and the middle labeled “normal”, see appendix B in study II.

The second step of the perceptual analysis started with two training trials where the listeners were presented with and rated speech samples from other individuals with neurological speech impairments not included in this study, in order to be familiarized with the procedure. The same group of listeners was then presented with samples of reading from the subjects with SCA. Ratings were made individually and listeners were
allowed to listen to the samples several times if needed. Definitions of all speech parameters were available in writing during the sessions. In study II, fourteen samples were duplicated to allow for analysis of intra-rater reliability. In study II there was also a third session, during which all speech samples from control subjects were rated.

The same protocol, developed for study II, was used again in study IV and the same group of expert listeners rated the speech samples. In this study, recordings from three different assessments of nine subjects included in the study were presented in random order and rated in one session (altogether 27 speech samples). Six of the speech samples were duplicated to allow for analysis of intra-rater reliability.

2.5 ASSESSMENT OF LANGUAGE AND COGNITION

A battery for assessment of language and cognition was compiled for assessment of subjects with SCA and control subjects in study III. The selection of test materials was motivated by several factors; to allow for an estimation of global cognitive function, to provide assessment of different aspects of language and cognition, to minimize test time. See table 7 for an overview of test materials and areas of assessment in study III.
Table 7. Test materials for assessment of language and cognition in study III

<table>
<thead>
<tr>
<th>Area of assessment</th>
<th>Test material</th>
<th>Task</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognitive function, FSIQ</td>
<td>Five subtests from the Wechsler Adult Intelligence Scale Revised, WAIS-R</td>
<td>Estimation of full scale intelligence quotient</td>
<td>Wechsler (1981)</td>
</tr>
<tr>
<td>Estimation of cognitive level</td>
<td>Swedish Lexical Decision Test, SLDT</td>
<td>Estimation of cognitive level</td>
<td>Almkvist et al. (in press)</td>
</tr>
<tr>
<td></td>
<td>Irregularly Spelled Words, ISW</td>
<td>Estimation of cognitive level</td>
<td>Tallberg et al. (2006)</td>
</tr>
<tr>
<td>Lexico-semantic knowledge</td>
<td>Information (WAIS-R)</td>
<td>Semantic and lexical knowledge</td>
<td>Wechsler (1981)</td>
</tr>
<tr>
<td></td>
<td>Similarities (WAIS-R)</td>
<td>Verbal abstraction</td>
<td>Wechsler (1981)</td>
</tr>
<tr>
<td></td>
<td>Boston Naming Test</td>
<td>Confrontation naming</td>
<td>Kaplan et al. (1983)</td>
</tr>
<tr>
<td></td>
<td>Swedish Lexical Decision Test, SLDT (# of words correct)</td>
<td>Lexico-semantic knowledge</td>
<td>Almkvist et al. (in press)</td>
</tr>
<tr>
<td></td>
<td>Irregularly Spelled Words, ISW (# of words correct)</td>
<td>Lexico-semantic knowledge</td>
<td>Tallberg et al. (2006)</td>
</tr>
<tr>
<td>Memory</td>
<td>Rey Auditory Verbal Learning Test (RAVLT)</td>
<td>Verbal memory (learning and retention) Short term memory and selective attention</td>
<td>Rey (1958)</td>
</tr>
<tr>
<td></td>
<td>Digit Span (WAIS-R)</td>
<td></td>
<td>Wechsler (1981)</td>
</tr>
<tr>
<td>Executive functions</td>
<td>Block Design</td>
<td>Visuospatial analysis – planning and organization Verbal fluency - Associative ability</td>
<td>Wechsler (1981)</td>
</tr>
<tr>
<td></td>
<td>Phonemic Fluency (FAS)</td>
<td></td>
<td>Benton and Hamsher (1989)</td>
</tr>
<tr>
<td></td>
<td>Stroop Color Word Test</td>
<td>Selective attention/ control</td>
<td>Golden and Freshwater (1998)</td>
</tr>
<tr>
<td>Motor speech</td>
<td>Speech rate, reading Stroop, word reading Sequential and alternating motion rates (SMR/AMRs)</td>
<td>Motor speed (speech)</td>
<td>Golden and Freshwater (1998)</td>
</tr>
</tbody>
</table>
2.6 STATISTICAL ANALYSIS

All statistical analysis was done using SPSS (version 11.0 and 14.0 for Windows). Statistical analysis included calculations of mean, standard deviations and coefficient of variation as well as t-tests to test for statistical significance. In study II Cronbach’s alpha was used to calculated inter-rater reliability of the ratings of perceptual parameters and in study IV Spearman’s rank correlation coefficient was chosen for this as well as for calculations of intra-rater reliability for ratings of perceptual parameters. Factor analysis by means of principal axis factoring and subsequent varimax rotation was also used in the analysis of perceptual data in study II. Pearson’s and Spearman’s correlations coefficients were also used in study II, III and IV. Finally, the Friedman test (a nonparametric equivalent of the one-way within-subjects analysis of variance) was performed in order to compare both perceptual and acoustic data between the three different assessments in study IV.

2.7 ETHICAL CONSIDERATIONS

The studies were reviewed and approved by ethical committees (Forskningskommitté Syd, dnr 288/01; Regionala forskningsetikkommitén Karolinska Institutet, 02-330; Regionala etikprövningsnämnden i Stockholm04-455/4 and the Human Research Protections Program, UCSD, project number 030369). Informed consent was obtained from all participants in the studies.
3 RESULTS

3.1 RELIABILITY OF PERCEPTUAL ASSESSMENTS

Reliability of perceptual assessments in study II and IV was found to be robust. In study II, mean inter-rater reliability was 0.84 and mean intra-rater reliability was 0.73 using Cronbach’s alpha. In study IV Spearman’s rank correlation coefficient was used, and mean inter-rater reliability was 0.60 whereas intra-rater reliability was 0.83. A few of the individuals with SCA from study II were also included in the longitudinal study (study IV). Their speech samples from the first assessment were thus re-rated by the same group of listeners approximately two years later when the perceptual assessment was done for study IV (during a session when all speech samples from assessments I, II and III were rated). This provided an opportunity to further evaluate the consistency within the judges, in this case with time interval of two years between ratings. It was found that intra-rater agreement was 0.79 between the first and second rating of these speech samples.

3.2 SPEECH AND VOICE CHARACTERISTICS IN SCA - PERCEPTUAL AND ACOUSTIC FINDINGS

The most salient perceptual characteristics in speech and voice in the subjects with SCA were found in three clusters of speech dimensions defined by Darley et al. (1969b); articulatory inaccuracy, prosodic excess and phonatory-prosodic insufficiency. Mean VAS ratings (mm) and standard deviations for the ten perceptual parameters with highest ratings are summarized in table 8. The speech parameters “imprecise consonants” and “imprecise vowels”, “equalized stress”, “monotony”, “stereotypic intonation”, “inappropriate silences”, “prolonged intervals”, “speech rate” and “degree of deviation” were rated statistically significantly higher for subjects with SCA compared to matched control subjects.
Table 8. Summary of mean VAS ratings (mm) for the ten most prominent perceptual parameters in 21 subjects with SCA. Clusters according to Darley et al. (1969b).

<table>
<thead>
<tr>
<th>Cluster</th>
<th>Perceptual parameter</th>
<th>Mean rating in visual analogue scale, VAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articulatory inaccuracy</td>
<td>Imprecise consonants</td>
<td>31.7 (23.9)</td>
</tr>
<tr>
<td>Prosodic excess</td>
<td>Equalized stress</td>
<td>36.4 (26.3)</td>
</tr>
<tr>
<td></td>
<td>Stereotypic intonation</td>
<td>22.4 (28.9)</td>
</tr>
<tr>
<td></td>
<td>Inappropriate silences</td>
<td>21.2 (26.3)</td>
</tr>
<tr>
<td></td>
<td>Prolonged intervals</td>
<td>17.8 (24.3)</td>
</tr>
<tr>
<td>Phonatory-prosodic</td>
<td>Vocal instability</td>
<td>28.9 (29.4)</td>
</tr>
<tr>
<td>insufficiency</td>
<td>Monotony</td>
<td>25.4 (30.4)</td>
</tr>
<tr>
<td></td>
<td>Strained strangled</td>
<td>25.0 (28.5)</td>
</tr>
<tr>
<td></td>
<td>Glottal fry</td>
<td>17.9 (17.2)</td>
</tr>
<tr>
<td></td>
<td>Harshness</td>
<td>17.5 (26.7)</td>
</tr>
</tbody>
</table>

A factor analysis of perceptual data was done and resulted in four factors with eigenvalues greater than one. These four factors explained 83.3% of the variance. Factor three and four only had one parameter with high factor loadings and were therefore considered less important. The first factor explained 50.9% of the variance and included speech parameters mainly related to durational aspects of speech production.

This factor was named “articulatory timing”. Several of the perceptual parameters in the first factor are directly related to temporal aspects of speech, e.g. “prolonged intervals” and “equalized stress”. Several parameters are also associated with prosody, e.g. “stereotypic intonation pattern”. “Monotony” also got a high loading in factor one (“articulatory timing”). The acoustic analysis showed that F0 range was not different between subjects with SCA and control subjects, and it can thus be assumed that the perceived monotony was due to temporal aspects rather than reduced pitch. It can also be hypothesized that the imprecision of consonants and vowels can be attributed to timing difficulties rather than neuromuscular weakness or difficulties reaching articulatory targets. Then all perceptual parameters in the first factor are related to temporal regulatory aspects of speech production and may reflect a common underlying neurophysiological deficit. These perceptual parameters may reflect motor speech programming impairment rather than motor speech execution deficits.
The second factor explained 14.8% of the variance and included perceptual parameters related to voice function. Harshness, strained-strangled and glottal fry had highest factor loadings and the factor was named “vocal quality”. The three perceptual parameters in the second factor all relate to vocal hyper-function and are also likely to be related to a common underlying neurophysiological deficit.

The third factor only included one parameter with a high factor loading (breathiness), but this parameter is strongly related to vocal hypo-function and may thus reflect an opposite aspect of vocal functioning, see figure 2.

Figure 2. Factor 1, 2 and 3 found in study II

Many aspects of the perceptual characterization of speech and voice in subjects with SCA were supported by the acoustic analysis. Speech rate was below normative data in one of the three subjects in study I and was found to be statistically significantly lower
than the speech rate of matched control subjects in study II. Also, sequential and alternating motion rates (SMR/AMR) were below normative data in study I and found to be significantly lower in subjects with SCA compared to matched control subjects in study II. The proportion speech/pause time was also altered in subjects with SCA in study I (increased pause time) compared to normative data, which may be reflected in perceived prolonged intervals and short phrases.

“Equalized stress” was the perceptual parameter that yielded the highest ratings on the VAS in subjects with SCA and there was a statistically significant difference in ratings for subjects with SCA and control subjects. Several of the acoustic measures relate to perceived equalized stress; e.g. syllable duration during SMR/AMR was not only increased, but also, as was shown in study II, more variable. This indicates difficulties in temporal regulation. Similar difficulties with temporal dysregulation was evident in the increased variability in the inter-stress intervals (ISIs) shown in study I. In both Swedish and English stress beats are expected at relatively equal intervals, and to achieve this, the speaker has to make temporal adjustments of syllable durations. In the subjects with SCA, the loss of temporal control resulted in more variable ISIs which is reflected in the increased ratings of the perceptual parameter “equalized stress”.

“Monotony” was yet another of the perceptual parameters that yielded one of the highest mean ratings on the VAS in subjects with SCA and a statistically significantly higher rating compared to control subjects. This perceptual parameter may also be related to difficulties with temporal control. As mentioned previously, the perceived monotony seemed to be due to temporal aspects, which have to do with the loss of temporal control, rather than reduced pitch range. It can also be argued that the perceived imprecision of consonants and vowels also are related to articulatory timing, i.e. speech motor programming abnormalities, rather than only reduced strength and range of movement, i.e speech execution deficits.

“Vocal instability” was one of the perceptual parameters with the highest mean rating on the VAS in subjects with SCA. This was confirmed by the measures of coefficient of variation (CV) of F₀ during sustained phonation. CV of F₀ was found to be increased in two of the three subjects in study I and it was shown to be statistically significantly increased in subjects with SCA compared to matched control subjects in study II. It is of interest to note that CV of F₀ during sustained phonation was markedly increased also in the two subjects with the mildest speech impairments in this investigation. One
of the subjects received a mean rating of degree of deviation of only 4 mm on the VAS and had a dysarthria score of 0.43 but still had a CV of F₀ of 7.9%. The other subject with very mild speech impairment had a mean rating of degree of deviation of 12.5 on the VAS and a dysarthria score of 0.19 but a CV of F₀ of 12.2%. The mean CV of F₀ in the group of control subjects in study II was 3.6%. This could indicate that the vocal instability may be one of the first signs of speech impairment, evident also when other aspects of speech are judged as within normal limits.

3.3 PROGRESSION OF SPEECH AND VOICE SYMPTOMS

The progression of speech and voice symptoms was followed in nine of the subjects over a time period of close to three years in study IV. Speech recordings used for perceptual and acoustic analysis and dysarthria assessments were done at three times during this time interval. A statistically significant increase of the mean dysarthria score was found. There were also statistically significant increases in perceived imprecision of consonants and perceived stereotypic intonation based on VAS-ratings.

Results of ratings of perceptual parameters were also analysed for subjects with early disease onset and late disease onset separately. It was noted that mean ratings of perceptual parameters related to speech function increased more between assessments in subjects with early disease onset compared to subjects with late disease onset. These were the same parameters that had high factor loadings in factor one “articulatory timing” in study II (except for the parameter “inappropriate silences” which had been excluded from the factor analysis due to skewness). The mean ratings of most speech parameters were higher than ratings of voice parameters in subjects with early disease onset. In the subjects with late disease onset, speech and voice parameters did not change much over the three assessments and ratings were also generally lower than in the group with early disease onset.

A few of the acoustic measures reached statistically significant changes, e.g., duration of /ta/ and /pa-ta-ka/ in rapid syllable repetition, variability of pause duration during rapid repetition of /pa/ and duration of inter-stress intervals (reflecting reduced speech rate). Several of the other acoustic measures also changed, there was e.g., a reduction of speech rate and an increase of duration of sustained fricative, the changes did however not reach statistical significance. Some acoustic measures were already markedly impaired compared to normative data, e.g., sequential and alternating motion rates.
but the small additional decrease of SMR/AMR that was noted also did not reach statistical significance.

3.4 LANGUAGE AND COGNITION IN SCA
Several aspects of language and cognition turned out to be impaired in the subjects with SCA compared to control subject. The most severe impairments were found in the areas of executive functions and attention. Performance in tasks requiring selective attention, control and flexibility like the Color/Word section of the Stroop test, Digit symbol from the WAIS-R and the Trail Making Test B were affected the most and results were statistically significantly lower than results by matched control subjects. Performance on the Block design and verbal fluency tasks were also severely impaired and statistically significantly below the result of the matched control subjects. Memory tasks and the language tasks (mainly assessing lexico-semantic knowledge) were also impaired but to a lesser degree. In addition, the subtests from the WAIS-R were used to estimate global cognitive function which was found to be markedly reduced and statistically significantly below the global cognitive function of the matched control subjects. When subjects were divided in two groups, based on their estimated global cognitive level, the subjects with the least cognitive impairment performed within the normal range on the lexico-semantic tasks and were less impaired on the memory tasks. Performance on tasks assessing executive functions, and attention were however very similar in the two groups and the motor speed performance was also similar despite level of global cognitive function. The global cognitive measure correlated significantly with age at disease onset, but not with disease duration. For several of the subjects in the group with less impaired global cognitive function the first symptoms were noted in the 6th decade of life, two of the subjects noted their first symptoms in their 4th decade and only one subject noted the first symptoms in her 3rd decade of life. In the group with more impaired global cognitive functioning, disease onset was in the 1st, 2nd or 3rd decade of life, and only a few of the subjects had noted their first symptoms at an older age than that. It is of interest to compare this finding with previous findings of correlations between age of onset and nucleotide repeat size (Cancel et al., 1997; Dürr et al., 1998)

3.5 SYMPTOM PROFILES
Nine of the individuals with SCA were included both in study II and III and were thus subject to both perceptual and acoustic analysis as well as assessment of cognition and
language. The results of assessment in all these different areas are summarized in Table 9.

Table 9. Symptom profile of individuals with SCA (n=9) assessed with both neuropsychological test battery and perceptual and acoustic speech/voice analysis

<table>
<thead>
<tr>
<th>Cognition</th>
<th>Lexico-semantic knowledge</th>
<th>++</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Executive functions</td>
<td></td>
<td>++</td>
</tr>
<tr>
<td>Attention</td>
<td></td>
<td>+++</td>
</tr>
<tr>
<td>Speech</td>
<td>Motor speed (acoustic)</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Rate of speech (perceptual)</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Speech parameters (perceptual)</td>
<td>++</td>
</tr>
<tr>
<td>Voice</td>
<td>Coefficient of variation of F0 (acoustic)</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>Voice parameters (perceptual)</td>
<td>+</td>
</tr>
</tbody>
</table>

Test results from neuropsychological assessment, including language, were transformed to z-scores. Data from acoustic analysis (rate of speech, syllable repetition rate and coefficient of variation of F0) were also transformed to z-scores. Results of the perceptual analysis were summarized for parameters related to articulation and timing (imprecision of consonants and vowels, equalized stress, short phrases, inappropriate silences, prolonged intervals, monotony and stereotypic intonation) and for parameters related to vocal quality (harshness, glottal fry, vocal instability, breathiness, strain-strangled, vocal tremor). Based on the z-scores and the mean VAS ratings, degree of severity was estimated in each area. For a z-score between 1-2, + was assigned. For a z-score between 2-3, ++ was assigned and for a z-score of 3 or higher, +++ was assigned. Similarly, degree of severity was estimated for the results of the perceptual assessments. For a mean VAS rating between 10-20 mm, + was assigned, for a mean VAS rating between 20 and 30 mm, ++ was assigned and for a mean VAS rating of 30 mm or higher, +++ was assigned.
The symptom profile shows that the areas most affected in these individuals are related to motor speed (rate of speech, rate of syllable repetition and also perceived rate of speech). It can also be noted that in the cognitive domain, attention is the most severely impaired area, followed by executive functions. Obviously, there are several components involved in the cognitive processing required to perform the tasks used to assess attention and executive function, but speed of processing is one of them. Possibly an underlying deficit affecting both motor and cognitive tempo may be involved in the symptoms observed in these patients. The symptom profile also summarizes that perceptual parameters related to vocal quality are less severely affected in these individuals with SCA than perceptual parameters associated with articulation and timing (speech motor programming).
4 GENERAL DISCUSSION

4.1 SUBJECTS

In this investigation different aspects of communicative functions were studied in a group of subjects with cerebellar degenerative disease. Most of the subjects were diagnosed with SCA using molecular genetic testing and several subtypes of SCA were represented in this group. Some of the subjects were however instead diagnosed based on clinical examination by a specialist in neurology, and neuroradiologic examination. It can be assumed that subjects who did not show a mutation in one of the known genes might still have SCA due to the fact that several genes remain to be discovered and thus can not be tested for. Obviously it can be argued that the group of subjects is heterogeneous and that this limits the conclusions that can be drawn from these studies. It would of course have been optimal to study groups with different subtypes of SCA separately and it would have been very interesting to define phenotypes and look for relationships between phenotypes and genotypes, which was the idea that initially sparked the interest in investigating different aspects of communicative functions in this population. It turned out however that recruiting high enough numbers of subjects with different subtypes of SCA to do phenotype/genotype comparisons was beyond what was feasible for the thesis project. It was still of value to characterize speech, voice, language and cognition in a group of subjects with cerebellar degenerative disease, since most descriptions of communicative dysfunction associated with cerebellar disease are based on more heterogeneous groups than that, including both cerebro-vascular disease, tumours, trauma and metabolic or toxic disorders. In addition, studies of language and cognition in cerebellar disease are still sparse.

4.2 RELIABILITY OF PERCEPTUAL ASSESSMENT

A comprehensive perceptual assessment of speech and voice in a group of subjects with SCA and matched control subjects was performed in this investigation. Perceptual assessments are sometimes considered too subjective and reliability has been questioned. This investigation includes several robust measures of inter- and intra-rater reliability. Mean inter-rater reliability was 0.84 and mean intra-rater reliability was 0.73 using Cronbach’s alpha in study II. In study IV mean inter-rater reability was 0.60 and intra-rater reliability was 0.83, calculated with Spearman’s rank correlation coefficient. It was also interesting to note that for some of the speech samples that were rated twice by the same group of expert listeners with an interval of close to two years between
ratings, the intra-rater reliability was still 0.79. These results indicate that the perceptual assessments in this investigation are quite reliable, both within and between the judges and also over an extensive period of time. Similar strong support for perceptual assessment methodology has also been found in many other studies, e.g., Hammarberg (1986); Sederholm et al. (1993); McAllister et al. (1994); Södersten et al. (1993).

It has been shown that training of judges in perceptual assessment and consensus on definitions of terminology are factors that are essential in order to obtain reliable results (Kent, 1996). In this investigation there was a training session in which speech samples from three individuals with neurological disease were rated and discussed by the expert listeners before the actual rating were started and definitions of terminology were reviewed. Possibly, more extensive training had resulted in even better reliability. In study II, the perceptual parameters “excessive variation of pitch” and “mixed nasality” had low inter- and intra-rater reliability and had to be excluded and in study IV the same two perceptual parameters and also the parameter “harshness” were excluded for the same reason. Both “excessive variation of pitch” and “mixed nasality” yielded low ratings and seemed to be present in only a few of the subjects with SCA, which probably contributed to the poor reliability measures. It can be assumed that these perceptual parameters are not very relevant in this population. The low agreement regarding the perceptual parameter “harshness” in study IV was probably more related to some confusion concerning terminology, and this is an example where more extensive training and/or more in-depth discussions in order to reach consensus on terminology may have made a difference. In study IV, “harshness” may have been confused to some degree with “glottal fry”, especially in one of the expert listeners who rather consistently rated the parameter “glottal fry” high when other judges rated “harshness” high. This confusion may relate to the terminology used. In Swedish, the term “harsh” voice is sometimes translated both with “skrapig” for more high-frequency aperiodicity and “skrovlig” for more low-frequency aperiodicity (Gentzel and Johansson, 1997). In this investigation, a combination of these two terms was used to describe “harshness” (“skrapig/skrovlig”) and the definition included both these aspects of aperiodicity. The term “skrovlig”, meaning low-frequency aperiodicity is closely related to glottal fry which may explain the lack of consensus. In future perceptual studies of speech in cerebellar disorders the distinction between “harshness” and “glottal fry” has to be clarified and exclusion of the parameters “excessive variation of pitch” and “mixed nasality” is suggested.
4.3 PERCEPTUAL FINDINGS

The perceptual characterization of speech and voice in subjects with SCA in this investigation is different in some ways from the classic description of ataxic dysarthria by Brown et al. from (1970). The most prominent speech dimension in the study by Brown et al. was “imprecise” consonants" whereas in this study “equalized stress” was clearly the most prominent perceptual parameter. The speech dimension “vowels distorted” was also prominent in the study by Brown, but in this study the corresponding parameter “imprecise vowels” was one of the parameters with the lowest ratings. Brown et al. commented that several dimensions, e.g “vowels distorted” frequently were absent in patients with mild impairment and possibly the difference reflects that subjects in the present investigation had less severe dysarthria. “Irregular articulatory breakdown” was the third most prominent dimension in the study by Brown, and this parameter was not included in the protocol for this investigation based on the initial session when relevant parameters were identified from speech samples of subjects with SCA and this parameter was not identified in any of the speech samples. “Monotony”, “prolonged intervals” as well as “reduced rate of speech” was prominent both in the study by Brown et al. and in this investigation. Also “harshness” was rated as prominent in the study by Brown et al. In the present investigation “glottal fry” and “harshness” was among the ten perceptual parameters with the highest ratings in study II, but the parameters “vocal instability” and “strained-strangled voice” were rated even higher. This may reflect that perceptual parameters associated with spasticity are more prominent in subjects with SCA compared to subjects with ataxic dysarthria secondary to other disorders. The component of spasticity may be related to the brainstem degeneration present in SCA, but is usually not present in other disorders resulting in ataxic dysarthria. A similar observation was made by Gilman and Kluin (1984) in a comparison between patients with Friedreich’s ataxia and patients with olivopontocerebellar degeneration. They noted that both groups shared several perceptual symptoms such as “slowness”, “dysrhythmia”, “excess and equal stress” and “prolonged phonemes and intervals”, whereas “strained-strangled harshness” and “low monopitch” only was present in patients with olivopontocerebellar degeneration but not in Friedreich’s ataxia.

Few other detailed perceptual studies of speech in subjects with cerebellar disease have been performed. In the study of ataxic dysarthria by Kent et al. (2000), three judges
rated four dimensions (vocal quality, intelligibility, prosody and severity), using a five point EAIS. They found mild to moderate impairment on the four rated dimensions. Joanette and Dudley (1980) performed an extensive perceptual study of speech in subjects with Friedreich’s ataxia. In their study three judges rated 16 speech dimensions in 22 speech samples from subjects with Friedreich’s ataxia. Several dimensions related to voice function were the most prominent in their study; “pitch level”, “pitch breaks” and “monopitch” were the three most prominent dimensions and “harsh voice” was ranked as number six, whereas “excess and equal stress” and “imprecise consonants” were not among the ten most prominent dimensions, which was different both from the description of ataxic dysarthria by Brown et al (1970) and findings in the present investigation. A factor analysis of the perceptual data resulted in two main factors; one was referred to as a “general dysarthric factor” and the second was referred to as a “phonatory-stenosis factor” and included dimensions related to increased tension and aperiodicity of function in the laryngeal mechanism. These factors resembled findings in study II in the present investigation.

4.4 ACOUSTIC FINDINGS
Several of the perceptual findings in this investigation were confirmed acoustically and were also in accordance with findings in other studies of ataxic dysarthria. Reduced speech rate was observed both perceptually and acoustically in this investigation. Rate reduction in ataxic dysarthria has also been reported in several other acoustic studies of ataxic dysarthria (Kent et al., 2000; Kent et al., 1997; Ackerman and Hertrich, 1994). Also reduced SMR/AMR is a common finding in ataxic dysarthria, reported e.g. by Portnoy and Aronson (1982) and Ziegler and Wessel (1996). The increased variability of syllable durations, which was hypothesized to relate to the perceptual parameters associated with prosodic deviation, has also previously been shown in ataxic dysarthria (Kent et al., 1979; Boutsen et al., 1997, Kent et al., 2000, Gentil, 1990). Also the increased variability of inter-stress intervals, ISIs have been reported in other studies of ataxic dysarthria, e.g. Hartelius et al. (2000).

Already in 1979, Kent et al. showed an increased variability of segment durations and also discussed that the variability increased with increased duration of segments in subjects with ataxic dysarthria compared to control subjects. There was however some overlap between control subjects with longer durations of segments and subjects with ataxic dysarthria with relatively normal segment durations. In the present investigation,
similar results were obtained in study I. Both ISI durations and ISI variability were increased in subjects with SCA, but again there was one of the control subjects with longer ISI durations who also had an increased ISI variability similar to the subjects with SCA and it could not be excluded that variability also may increase in normal speakers using a reduced speech rate. To investigate this issue, a group of eight speakers with no neurological impairment were asked to produce the ISI sentences in both normal speaking rate and in a slow speaking rate and ISI durations and ISI variability were measured. There was a statistically significant difference between durations of ISIs between the two speaking rates, but there was no statistically significant difference in CV of ISI duration. This minor experiment supports the fact that the increased durational variability is a specific feature in subjects with cerebellar disease and not just a result of reduced rate of speech per se, see figure 3.

![Inter-stress intervals (ISIs) in normal and slow rate of speech (n=8)](image)

Figure 3. Duration and variability of inter-stress intervals (ISIs) in healthy speakers using normal rate of speech and slow rate of speech.

The long-term phonatory instability related to the perceived vocal instability found in the present investigation resembles findings from other studies of ataxic dysarthria, e.g. Kent et al. (2000). King et al. (1994) found that measures of long-term phonatory instability were useful in demonstrating the decline of function in longitudinal studies of patients with Parkinson’s disease. In the longitudinal study in this investigation, the
CV of $F_0$ was higher than what can be expected in normal speakers, but did not change over the period time covered in the study. Possibly, this measure may still be indicative of decline of vocal function, but need to be studied over a longer time period and in a larger group in this population. Also, in general, perceptual parameters associated with vocal function seemed to change less in this small group of subjects than aspects of speech production such as duration and variability of speech segments and measures related to prosody.

4.5 PROGRESSION OF SPEECH AND VOICE SYMPTOMS

In study IV, the progression of speech and voice symptoms was studied with perceptual and acoustic methodology. It was found that the perceptual parameters “imprecise consonants” and “stereotypic intonation” were rated statistically significantly higher over the time period of close to three years. Changes in speech and voice symptoms were more substantial in subjects with early disease onset compared to disease onset later in life, regardless of disease duration. Only nine subjects participated in this study, which obviously is a very small number and limits the conclusions that may be drawn. Very few longitudinal studies of speech and voice in neurodegenerative disorders are at all available in the literature, and the few studies that have been done also have very small numbers of participants. It was still of interest that significant changes could be observed both with perceptual and acoustic methodology in this small number of subjects over a relatively short period of time. Longitudinal studies of large groups of subjects are hard to perform, not the least due to difficulties funding such long-term work, but the findings from study IV indicate that these kinds of studies may generate valuable information. Little is known about the progression of symptoms and this information is important not the least from a clinical perspective in assisting patients in counteracting the increasing disabilities caused by their disease.

4.6 LANGUAGE AND COGNITION IN CEREBELLAR DISEASE

Significant decline of several aspects of cognition and language was observed in subjects with SCA compared to control subjects, impairment of executive functions and attention being the most severely affected. Several other studies of cognition in subjects with SCA have reported executive dysfunction (Maruff et al., 1996; Storey et al., 1999; Bürk et al., 1999; Bürk et al., 2001; Gambardella et al., 1998; Stone et al., 2001; Le Pira et al., 2002; Zawacki et al., 2004). In some other studies impaired attention has also been found (Maruff et al., 1996; Le Pira et al., 2002; Zawacki et al., 2002; Lilja et al.,
Different aspects of memory have also been investigated in some studies of cognition in SCA and impairment of both verbal memory and visuospatial memory have been found. Bürk et al. (1999, 2001), Le Pira (2002) and Kawai et al. (2004) reported impairment of verbal memory but not visuospatial memory. Maruff et al. (1996) found visual memory to be normal, whereas Kawai et al. (2004) also found visual memory deficits and similar findings were reported by Stone et al. (2001). Semantics has been studied less often, but a few reports of reduced verbal skills have been published, e.g. Lilja et al. (2005). The slight impairment in lexical-semantic knowledge reported in study III, and the observation of more severe impairment in subjects with low estimated global cognitive functioning, has not been extensively reported before. This finding contributes to a more detailed characterization of cognition, including language functions, in subjects with SCA. The differences in symptom-profiles between subjects with more impaired estimated global cognitive functioning and less impaired estimated global cognitive functioning, showing that executive functions and attention are impaired in subjects in both groups, whereas lexical-semantic knowledge only is affected in subjects with more severely impaired global cognitive function is also a new finding with clinical implications. Whether the impairment in cognition and language found in subjects with SCA in the present study were due to cerebellar degeneration per se, or if dysfunction was related to a disruption at some other level of the cerebro-cerebellar circuitry can not be concluded from these data. Continued studies, including neuro-imaging may be able to address this question in the future. The findings from the present investigation do however have direct clinical implications. Patients with SCA need more extensive evaluations also of cognition and language, and may also need intervention aimed at developing compensatory strategies to handle e.g. memory dysfunction, word retrieval difficulties and attention deficits.
4.7 SUMMARY AND CONCLUSIONS

Speech in the individuals with SCA in this investigation was perceptually mainly characterized by equalized stress, imprecise consonants, vocal instability, monotony, strained-strangled voice, stereotypic intonation and reduced speech rate.

Factor analysis of perceptual parameters resulted mainly in two factors; one included parameters related to temporal durational aspects of speech, called “articulatory timing” and the other included parameters related to vocal function. The perceptual parameters in this factor were associated with vocal hyper-function, which may be due to an element of spasticity present in these subjects. The third factor consisted of the perceptual parameter breathiness and was related to vocal hypo-function.

Acoustic analysis confirmed the perceptual findings. Rate of speech and sequential and alternating motion rates, SMR/AMRs were statistically significantly reduced and duration and variability of syllables and pauses in SMR/AMR were increased. Also, duration and variability of inter-stress intervals (ISI) were both increased in individuals with SCA.

Mean fundamental frequency and range during text reading was not different in individuals with SCA compared to matched control subjects. Mean $F_0$ during sustained phonation was also not different in this group of individuals with SCA compared to matched control subjects, but coefficient of variation (CV) of $F_0$ (a measure related to perceived vocal instability) was statistically significantly higher in individuals with SCA. Increased $F_0$ of CV was observed in subjects with SCA with very few other observed speech and voice symptoms and may be useful in early diagnosis.

In a longitudinal study of a group of individuals with SCA it was found that there was a statistically significant increase in perceived imprecision of consonants and stereotypic intonation over a time period of close to three years. There were also increases in ratings of many other perceptual parameters, especially parameters related to temporal aspects of speech production, as well as in other acoustic measures such as duration of sustained vowel or fricative, however these changes did not reach statistical significance. The mean dysarthria score also increased significantly over the 33 months of the study. Changes were larger, and perceptual parameters related to speech rather
than voice were more affected in individuals with early disease onset compared to late disease onset, regardless of disease duration.

Impairment of cognition and language was also found in this group of individuals with SCA compared to a group of control subjects matched for age, gender, length of education and estimated pre-morbid cognitive level. Executive functions and attention were impaired the most, but there were also statistically significant differences in performance on memory tests and one of the subtests assessing lexico-semantic function. When individuals with SCA were divided in two groups based on estimated global cognitive function, it was shown that individuals with low estimated global cognitive function also had lexico-semantic impairment, whereas the group with less affected global cognitive function did not show lexico-semantic impairment. Executive functions and attention were however affected also in individuals with less severely impaired global cognitive function.

By comparing different aspect of communicative functions assessed in this investigation it can be concluded that motor speed is most severely affected (as was shown by the reduced rate of speech and reduced SMR/AMR and in perceptual assessment of different parameters related to speech). However, in the cognitive domain, attention and executive functions are most severely impaired, and possibly this also reflects a more general defect of reduced speed of cognitive processing which is more crucial for cognitive processing in these tasks compared to tasks assessing e.g lexical-semantic knowledge and memory.

4.8 CLINICAL IMPLICATIONS AND FUTURE RESEARCH
Perceptually, the prosodic changes, reduced speech rate and harsh vocal quality are similar to findings from previous perceptual studies of ataxic dysarthria. Perceived vocal instability and strain-strangled vocal quality were however higher than in previous studies, and symptoms of vocal hyper-function may be indicative of spinocerebellar ataxia (SCA) as opposed to ataxic dysarthria of other etiologies. This investigation supports that detailed perceptual analysis by trained judges is reliable and clinically useful method of characterizing speech in neurodegenerative disease. In future studies, it would be of interest to investigate if differences in perceptual profiles can be found e.g in speech from subjects with SCA, Friedreich’s ataxia and MS.
The perceptual characterization may be of importance for treatment of speech and voice. Although SCA is a degenerative, progressive disease, intervention possibly focusing on respiratory support, coordination of respiration and phonation and improving vocal function may be useful for patients in optimizing their resources. Treatment studies of this nature would also be of great interest and clinical importance.

In addition, this investigation also adds to growing evidence of the role of speech and voice in neurological disease. The kind of detailed speech and voice analysis that was carried out in this investigation can be a useful tool as an indicator of treatment effect, e.g. in studies of pharmacological or surgical treatments.

The results in study III show the importance of assessment of cognition and language in this group of patients, which is usually not a clinical routine at present. With more detailed assessment of patients with SCA in this area, appropriate interventions to compensate for these difficulties may also be developed. Cognition and language in cerebellar disease is a relatively new area which needs further, detailed studies. Future studies of the relationship e.g. between trinucleotide repeat length and clinical symptomatology is of interest, as well as continued studies of the relationship between genotype and phenotype in different SCA subtypes and studies including neuro-imaging results and more detailed neurological examinations.

Finally, longitudinal studies of speech, voice, language and cognition in larger groups of subjects with SCA over extensive period of time are lacking and would be of great importance in gaining more knowledge about disease progression.
5 ACKNOWLEDGEMENTS

Many people have contributed to this investigation in several ways over the last years. I especially with to thank the following:

All the individuals with cerebellar disease who participated in the investigation. For your generosity and patience enduring all kinds of speech, language and neuropsychological testing and for sharing your experiences of living with cerebellar disease. Thank you also to all control subjects who participated.

Lena Hartelius, my main supervisor and co-author, for taking on long-distance supervision and for doing it in such a way that distance never was a problem. Because of your knowledge in motor speech disorders, your sharp, analytic mind, your wide perspectives and your friendly, generous personality it has always been a privilege and a lot of fun to have you as a supervisor.

Britta Hammarberg, my co-supervisor and co-author. Your enthusiasm and energy never cease to amaze me. You were one of my teachers and supervisors when I first entered the field of Speech-Language Pathology and you have continued to guide me in my professional life and through my doctoral studies. Thank you for always being so supportive, thanks for many laughs, thanks for sharing your vast knowledge and finally, thank you for caring so much about science and speech-language pathology but also about the children.

Ing-Mari Tallberg, co-author and colleague. Thank you for all your contributions. I will never forget our car trips around Sweden during our ventures to examine subjects with SCA, through snow storms in the winter and through beautiful sunny landscapes in the spring. Thank you for a lovely time at the cottage.

Maria Södersten, Helena Johansson, Lena Hartelius and Britta Hammarberg, knowledgeable colleagues, who contributed with “expert ears” during long sessions of perceptual evaluations.

Jody Corey-Bloom, Erik Björck and Atle Melberg for generous help with recruiting subjects for the studies. Jody also for supporting me in the US part of the investigation.
Joakim Westerlund and Ove Almkvist for expert advice regarding statistical analysis.

Eva Holmberg, for revising my English and for many insightful and constructive comments during seminars and presentations through these last years.

Per Östberg, colleague and fellow doctoral student, thank you for sharing your impressive knowledge on the brain and language (among many things) during inspiring talks. Thank you also for your kind contribution with “last-minute” illustrations.

Kerstin Johansson, my dear colleague and friend, thank you for sharing excitement and frustration through the years. Thank you also for always being so encouraging and for all your brilliant comments and ideas.

Kjerstin Greve-Löberg, Gunilla Henningsson, Marion Lieberman and Annika Sääf-Rothoff, my colleagues and friends in ”KI-gänget”. I feel very fortunate to have such friendly, supportive and inspiring colleagues to work with, and thank you for “covering” for me during my leave of absence for research.

All colleagues and friends in the Speech-Pathology Clinic at the Karolinska University Hospital, thank you for kind support, for collegial exchange and a friendly atmosphere in the clinic.

Christina Persson, Britt-Mari Tysk, Camilla Welander, Helene Lindqvist and Claire Johansson, for all kinds of practical help during the years and for generous assistance in the recording studio.

Hans Larsson, research engineer, for generous and patient technical assistance and for preventing several computer-related mental breakdowns through the years.

Svante Granqvist, for rapid e-mail support regarding SWELL-questions.

Helena Bergström, my dear friend, Klara’s Godmother, for all our interesting talks and walks through the years, for never being judgemental and for your support.
Catharina Stedt, dear old friend from “logopedlinjen”, for your lovely sense of humor, support and friendship.

Lilian Wikström and Dan Henningsson, neighbours and friends from Boston and Spånga, for caring and often offering a helping hand and for always being ready for a chat during late evening dog-walks.

Ludde, for late evening dog-walks.

All other friends, frequently and less frequently seen, for bringing joy, music, colour, flavour and spice to life.

Malin Wångstedt, Erik’s babysitter and “honorary family member” in 2002/2003, when I first embarked on this research project. Thank you for taking such good care of Erik when I was working and for being such a positive influence on the girls. I never had to worry!

My mother Keth Thelaus and my siblings Torbjörn, Annika and Jonas Thelaus and their families, for encouragement, for caring, for great family dinners, and for sometimes asking what it really is that I actually work on.

Warm thoughts go to the memories of my father, Erik Thelaus, and my mother-in-law, Daisy Schalling, for being sources of inspiration in writing and in science.

Kurt Schalling, my father-in-law, for being a wonderful grand-père and for always being supportive, and Sonja Mueser, for being a source of inspiration and showing that it is possible to pursue a doctoral degree after having several children.

Last, but not least, my dear family; thank you Martin for love, support and interesting and fun discussions about genetics and research and for making me aware of the interesting world of SCA, but also for being good at pulling me from work to do other interesting and fun things. Cajsa, Linnea, Klara and Erik, for being such wonderful, interesting people, and for bringing so much joy into my life. Also, thank you for all your contributions during these last months (not the least in the domestic arena) to the latest family project called “Mummy-disp-07”!
I gratefully wish to acknowledge the financial support for this investigation by the Board of Research for Health and Caring Sciences, the Centre for Hearing and Communication Research, the Aina Börjesson’s Foundation for Research in Speech-Language Pathology and the Department of Clinical Sciences, Intervention and Technology at the Karolinska Institutet as well as the Norrbacka-Eugenia Foundation for Research and the Swedish Association of Persons with Neurological Disabilities, NHR.
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