Working Memory in Adults with Prader-Willi Syndrome

A pilot-study based on CogState related to recent literature

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Thesis

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Summary

The Prader-Willi syndrome is a rare, complex, and genetically determined neurodevelopmental disorder. The subjects have their own individual characteristics; however share in common particular physical features and specific cognitive strengths and weaknesses. These change across the lifespan and make up the physical and behavioural “phenotype” of the syndrome. Learning difficulties are common and range the whole spectrum, from mild to severe. Most subjects find reading, spelling and especially mathematics very difficult. With age, certain behaviours become more evident, for instance repetitive and ritualistic behaviour in older children and adults. According to the literature subjects score moderate to high on subscales measuring compulsory behaviour. The literature on cognitive functioning and achievement of individuals with PWS is heterogeneous, concerning the pedagogical and psychological aspects in adults, the literature is sparse.

This study was based on individuals with genetically verified PWS included in the Nordic Prader-Willi study. By means of a computer based cognitive test (CogState), the aim of the present pilot study was, on a cross-sectional basis, to analyse aspects of the adults working memory. Further to relate the findings to existing literature concentrating on cognitive aspects of the syndrome and especially discussing aspects of working memory. Moreover, reflections concerning life long development and learning were based on the results. We found that adults with PWS have significantly decreased elements of working memory compared to normative data. In general, the subjects had median scores within two standard deviations below the normal mean, however with huge differences between the tests performed. Moreover, extensive inter-individual ranges were observed. Females did significantly better than male participants in some of the items. Related to BMI, the more obese had a slightly better performance of working memory than the less obese.

In conclusion, adults with PWS were both positive and corporative, in this time limited, motivating, and visual based cognitive test situation. In general; the sample had markedly decreased working memory, as detected with the CogState battery. The impairment for all items was of major magnitude, however the impairment of visual memory was less pronounced. This should be taking into account, when teaching strategies and learning are considered. The visual pathway is obviously the best functioning and should be used in educational settings and when giving general information.
Acknowledgements

This work is dedicated to my unofficial mentor Christian Aashamar, former headmaster and pedagogical and psychological counsellor at Frambu Competence Centre, who suddenly and unexpectedly passed away all too early, in the late summer 2006. Christian was an enthusiastic international capacity in the field of pedagogic research in the Prader Willi syndrome, and a true friend and supporter for all the Norwegian individuals with the syndrome and their families.

He introduced me to the Nordic Study of Adults with Prader Willi Syndrome and encouraged me to elaborate and complete part of the protocol as my master thesis.

I want to express gratitude to all individuals of the study and their families. Without their cooperation, interest and support, it would never have been possible to complete the study.

A special thank also to my supervisors, assistant professor Elisabeth Grindheim and post doc. Arne Ola Lervåg for their valuable advice, support and important academic discussions. I am grateful for the interest, help and support from Frambu Competence Centre, where the tests were conducted, and in particular to Gunn Petersen and Kai Fredrik Rabben M.D., for unrestricted help and cooperation.

I want to thank Tove Lekva, Section of Endocrinology, Rikshospitalet, Oslo for help with statistics and figures. I am obliged to Clinical Scientist Marina Falleti at CogState, Melbourne for providing me the normative data. Moreover, Marina has been very supportive with interpretation of the data and giving guidance in the writing process.

Finally, I am indebted to my husband Jens, and our four children for encouragement, help and support throughout the entire study and writing process, and especially for being close to me when hard work, frustrations and tears became too much.
List of abbreviations

ACC: Accuracy
AHUS: The University Hospital in Akershus
BMI: Body Mass Index
CE: Central Executive
DET 1/DET 2: Detection
df: Degrees of Freedom
EDS: Excessive Daytime Sleepiness
GH: Growth Hormone
IDN: Identification
IOP: Individuell opplæringsplan
IQ: Intelligence Quotient
LTM: Long-Term Memory
MON: Monitoring
OCL: One Card Learning
ONB: One Back Learning
PRD: Prediction
PWS: Prader-Willi Syndrome
RTV: Rikstrygdeverket
SD: Standard Deviation
STM: Short-Term Memory
STS: Short-Term Store
UPD: Uniparental Disomy
WM: Working Memory
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1. A general introduction to Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is named after two Swiss paediatricians, Dr Andrea Prader and Dr Heinrich Willi, who first described the syndrome in medical journals in 1956 (Prader et al. 1956). Sometimes it is referred to as “Prader-Labhart-Willi syndrome”, but the middle name, referring to the third Swiss paediatrician of the team, Alexis Labhart, is rarely used outside the German speaking countries. The syndrome has nonetheless, existed long before it scientifically was described. Two paintings which most certainly are of young girl with PWS exist in Spain. They are both to be found in the Museo del Prado in Madrid and are called “la Monstrua” and “Eugenia”. They are painted by the artist Juan Correno de Miranda at approximately 1680.

The British doctor, J. Landon Down, who first described Down syndrome in 1866, published a paper in 1864 in which he described a woman who had all the characteristics, which today is recognised as clinical criteria for PWS (Ward 1997).

The Prader-Willi syndrome is a relatively rare, complex, and genetically determined neuro-developmental disorder. Individuals with the syndrome have their own individual characteristics, yet they share particular physical features as well as specific cognitive strengths and weaknesses. They are likely to have particular behaviours and mental health problems in common. These change across the lifespan and together they make up the early and later physical and behavioural “phenotype” of the syndrome.

1.1 Prevalence of PWS

It is uncertain how many people worldwide are to be found with PWS. The first Consensus Diagnostic Criteria symposium reached agreement on the incidence of PWS as roughly 1:10,000 births and it is assumed that the prevalence is generally quoted to be between 1:15,000 and 1:25,000 (Holm et al. 1993). Thus, the expected longevity of individuals with PWS in Western societies is estimated to 40-50 years. PWS occurs equally distributed in both sexes and all races (Cassidy 1997).
In Norway approximately three to five children every year are born with the syndrome. There are no differences related to gender in the birth rate and today the Norwegian PWS population counts almost 120 persons (Landsforeningen for Prader-Willi syndrome 2005).

1.2 The main Characteristics of the Syndrome

PWS is as mentioned, a very complex condition which affects each individual differently. However, as more people were reported and research on the syndrome moved forward, the Consensus Diagnostic Criteria were revised. The reconsideration includes the main characteristics which are found to be present, in at least to some degree, in the majority of people who carry the syndrome (Holm et al. 1993). The final criteria of characteristics were divided into three groups: Eight major, eleven minor and eight supportive findings (Table 1).

1.3 Common Behavioural and Physical Features

The syndrome is today considered as a multistage disorder characterized by two or three different phases, depending on classification used (Holm et al. 1993; Whittington and Holland 2004d; Zellweger 1988).

The hypotonic phase is characterized by varying degree of floppiness at birth, very sleepy babies having a week cry and poor suck reflex, which often gives feeding difficulties, often requiring tube feeding. Undiagnosed, the mortality is very high, explaining why the syndrome is seldom described in developmental countries. The hypotonia lasts livelong, but is especially pronounced during the neonatal period and until the child is about two years of age. During this first phase the infants mainly are described as friendly, even-tempered and devoted (O'Brien and Yule 1995).
### Table 1. Published Diagnostic Criteria for PWS, (Holm et al. 1993)

**Major Criteria:**
1. Neonatal and infantile central hypotonia with poor suck, gradually improving with age
2. Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive
3. Excessive or rapid weight gain on weight-for-length chart (excessive is defined as crossing two centile channels) after 12 months but before 6 years of age; central obesity in the absence of intervention
4. Characteristic facial features with dolichocephaly in infancy, narrow face or bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip, down-turned corners of the mouth (3 or more are required).
5. Hypogonadism—with any of the following, depending on age:
   a. Genital hypoplasia, (male: scrotal hypoplasia, cryptorchidism, small penis and/or testes for age (<5th percentile); female: absence or severe hypoplasia or labia minora and/or clitoris
   b. Delayed or incomplete gonadal maturation with delayed pubertal signs in the absence of intervention after 16 years of age (male: small gonads, decreased facial and body hair, lack of voice change; female: amenorrhea/oligomenorrhea after age 16)
6. Global developmental delay in a child <6 years of age; mild to moderate mental retardation or learning problems in older children
7. Hyperphagia/food foraging/obsession with food
8. Deletion 15q11-13 on high resolution (>650 bands) or other cytogenetic molecular abnormality of the Prader-Willi chromosome region, including maternal disomy

**Minor Criteria:**
1. Decreased fetal movement or infantile lethargy or weak cry in infancy, improving with age
2. Characteristic behavior problems—temper tantrums, violent outbursts, and obsessive-compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required)
3. Sleep disturbance and sleep apnea
4. Short stature for genetic background by age 15 (in the absence of growth hormone intervention)
5. Hypopigmentation—fair skin and hair compared with family
6. Small hands (<25th percentile) and/or feet (<10th percentile) for height age.
7. Narrow hands with straight ulnar borders
8. Eye abnormalities (esotropia, myopia)
9. Thick viscous saliva with crusting at corners of the mouth
10. Speech articulation defects
11. Skin-picking

**Supportive Findings:**
1. High pain threshold
2. Decreased vomiting
3. Temperature instability in infancy or altered temperature sensitivity in older children and adults
4. Scoliosis and/or kyphosis
5. Early adrenarche
6. Osteoporosis
7. Unusual skill with jigsaw puzzles
8. Normal neuromuscular studies

To score, major criteria are weighted at 1 point each, and minor criteria are weighted at 1/2 point each. Supportive findings increase the certainty of diagnosis but are not scored. For children 3 years of age or younger, 5 points are required, 4 of which should come from the major group. For children >3 years of age and for adults, a total score of 8 is required and major criteria must comprise 5 or more points of the total score (Holm et al. 1993).
The second phase is the hyperphagic. Of significance in this phase is the growing interest for food that arises in the toddler. This is related to all kind of food items and varies from talking about food or focusing on the next mealtime to actively trying to obtain food by any means possible. The obsession often results in early onset of childhood obesity and physical inactivity. Together with the change in eating pattern the youngsters show poor socialisation skills, significant maladaptive behaviour and emotional characteristics. Among other findings temper tantrums, inappropriate social behaviour, auto-mutilation, depression, anxiety, obsessive-compulsive symptoms and exceptional skills, which resemble “splinter skills”, are described (Clarke et al. 2002; Dimitropoulos et al. 2001; Dykens 2002). Research findings report of individuals with PWS outperforming both with age and IQ-matched peers with mixed mental retardation and age-matched normal children with average IQs on jigsaw puzzle tasks, Table 1 and 3 (Dykens 2002).

Excessive daytime sleepiness (EDS) often is reported when describing characteristics of individuals with PWS. It is found to be correlating with severity of behavioural disturbance (Clarke et al. 1989). Some research suggests that this well-established clinical diagnostically criteria might be due to a disturbed and interrupted night’s sleep caused by sleep apnoea (Butler et al. 2002), others suggest that EDS is a primary feature of PWS rather than a consequence of too little and erupted night’s sleep (Vgontzas et al. 1996).

Learning difficulties are very common and range the whole spectrum, from mild to severe, see Table 1. Most subjects find reading, spelling and especially mathematics very difficult (Whittington et al. 2004a).

The third phase describes adolescence and adulthood in which health problems secondary to obesity become dominant. Scoliosis, dental problems, diabetes mellitus, respiratory infections, fractures and hypertension are dominant features as late manifestations (Butler et al. 2002).

With age, certain behaviours become more evident. These comprise confusion, withdrawnness and overtiredness. Especially British research has discovered that a large percentage of subjects with PWS in adulthood develop major psychiatric illness (Whittington and Holland 2004d).
### Table 2. Documented Diagnostic Criteria and Sensitivity in PWS

<table>
<thead>
<tr>
<th></th>
<th>Documented (%)</th>
<th>Sensitivity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal Hypotonia</td>
<td>87.9</td>
<td>97.5</td>
</tr>
<tr>
<td>Feeding problems in Infancy</td>
<td>77.8</td>
<td>95.7</td>
</tr>
<tr>
<td>Excessive weight Gain</td>
<td>66.7</td>
<td>95.0</td>
</tr>
<tr>
<td>Facial Features</td>
<td>88.4</td>
<td>49.4</td>
</tr>
<tr>
<td>Hypogonadism</td>
<td>51.1</td>
<td>95.6</td>
</tr>
<tr>
<td>Developmental Delay</td>
<td>98.9</td>
<td>97.8</td>
</tr>
<tr>
<td>Hyperphagia</td>
<td>84.4</td>
<td>93.4</td>
</tr>
<tr>
<td><strong>Minor Criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Fetal Activity</td>
<td>62.2</td>
<td>89.3</td>
</tr>
<tr>
<td>Behavior problems</td>
<td>86.7</td>
<td>82.1</td>
</tr>
<tr>
<td>Sleep disturbance/sleep apnea</td>
<td>75.6</td>
<td>36.8</td>
</tr>
<tr>
<td>Short stature</td>
<td>63.3</td>
<td>86.0</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>73.3</td>
<td>47.0</td>
</tr>
<tr>
<td>Small hands and/or feet</td>
<td>87.8</td>
<td>74.7</td>
</tr>
<tr>
<td>Narrow hands/straight ulnar borders</td>
<td>82.2</td>
<td>69.0</td>
</tr>
<tr>
<td>Eye abnormalities</td>
<td>67.8</td>
<td>49.2</td>
</tr>
<tr>
<td>Thick viscous saliva</td>
<td>88.9</td>
<td>82.5</td>
</tr>
<tr>
<td>Articulation defects</td>
<td>80.0</td>
<td>93.1</td>
</tr>
<tr>
<td>Skin-picking</td>
<td>83.3</td>
<td>61.3</td>
</tr>
</tbody>
</table>
Older children and adults exhibit behaviour that is repetitive and ritualistic. According to the literature they score moderate to high on several compulsivity subscales. Children with PWS both are found to exhibit higher rates and more types of compulsive disorder compared to children with for instance Down syndrome, other children with non-specific mental retardation and typically developing peers (Dimitropoulos et al. 2001; Dykens et al. 1996).

It has been theorized that the obsessive-compulsive symptoms are part of the behavioural phenotype that is related to a deletion on chromosome 15 (Hall and Smith 1972).

Many subjects with PWS have some physical resemblance in common. The physical features however, are not so different from the general population that they are striking. This means that a person with no awareness of the syndrome hardly would be able to single them out.

The characteristic features are described already in the earliest research dealing with the physical features of the syndrome (Hall and Smith 1972). Individuals born with the syndrome tend to have lighter hair, eyes and tan compared to the rest of their family. This is often referred to as “fair for families”. Their faces are often narrow with poor mimical expression. Their eyes are often almond shaped and the mouth down-turned.

Generally, their developmental milestones are delayed (Table 1 and 2). In adulthood individuals with PWS are shorter when full-grown compared to their siblings. Their hands and feet are smaller and shorter and often both men and women do not produce an adequate amount of sexhormones to develop maturity.

1.4 Mortality

In previous PWS literature there is an obvious lack of old and elderly people represented. Some studies have documented several elderly individuals, but the diagnosis of these subjects has been made only on clinical basis. One exception makes a genetically verified lady that died in the high age of more than 70 years (Carpenter 1994). Previously, individuals with the syndrome might have died early of secondary diseases related to hypotonia and/or obesity.

Today, as the diagnosed individuals are kept on a strict diet their weight and obesity related diseases are held within a reasonable and manageable level. Providing no complicating
medical conditions occur, individuals today can live into middle age and beyond. Nevertheless, sudden deaths and a linear increased mortality rate across the age range compared to the general population is described in literature (Butler et al. 2002; Whittington and Holland 2004c).

Even though the majority of literature and research related to the syndrome of PWS is written within the latest decades, it still suffers from serious methodological restraints and faults.

Only since the mid-eighties, scientific and technical progress made it possible to work with genetics verification on the sophisticated level, we are dealing with today. Thus, studies performed in the seventies and early eighties had to rely primarily on the clinical and the behavioural features when investigating the syndrome (Table 1). As a result, much of this literature might have drawn conclusions on doubtful evidence, especially because some individuals with learning disabilities in many clinical and behavioural aspects encompass great resemblance to subjects with genetically verified PWS.

Moreover, even recent studies are often conducted with a combination of self-selected subjects or participants included on behalf of merely clinical criteria. In other studies, research is based on information retrieved from the family or main carers (Butler et al. 2002).

1.5 Genetics of PWS

Within the last decades great progress has been made in our understanding of the genetics of PWS. Since the beginning of the 1980-ties it has been well-known that the syndrome is linked with an abnormality of the long arm of chromosome 15. Now called the PWS critical region and denoted by the term 15q11-q13, indicating that the deletion is between bands 11 and 13 on the chromosome (Whittington and Holland 2004a). It is current knowledge that the syndrome can be caused in several ways; all involve however, some missing information from the genes, which are found in the father’s chromosome 15.

There are two genetic manifestations of PWS; one is called deletion, the other disomy or maternal disomy. In the first case a small piece of the gene is missing on the chromosome 15, the child has inherited from the father. In the latter situation, the child has inherited two
chromosomes 15 from the mother, instead of one from each parent. The chromosome error arises by chance at or very near conception, even though the mother’s and the father’s chromosomes are perfectly normal. Only extremely atypical, there is a possibility of recurrence and inheritance of the syndrome.

The genetically verified cases of PWS caused by a deletion of the paternal chromosome constitute approximately 60% in recent series, maternal disomy is found in 30-35% of the cases. The remaining, usually less affected individuals, have other minor chromosomal errors, as for example micro-deletion or translocations (Dimitropoulos et al. 2000; Whittington and Holland 2004a). Thus, approximately two thirds of the cases are caused by paternal deletions and less than one third by uniparental disomy (UPD).

### 1.6 Phenotypic Differences between the Genetic Subtypes

The literature describes relatively few and mild differences between the major genetic subtypes of PWS. Especially, when compared with the wide inter-individual differences among subjects with PWS and when individuals with PWS are compared to controls (Cassidy et al. 1997; Whittington and Holland 2004a). The cohorts investigated are often small and thereby with a considerable risk of type 2 errors (Whittington and Holland 2004d). Moreover, the relative number of disomies varies and might be lower than so far described.

Based on the previous studies, describing and comparing the two major genetic subgroups, features in individuals with deletion or UPD can be divided into five general topics. These cover differences at birth, developmental, physical, behavioural, and cognitive differences, see Table 1.

Compared with normal babies, the individuals with PWS have lower birth weight and shorter body length; yet, comparisons between the genetic subgroups have not resulted in consistent differences. A lower birth weight in babies with deletion compared with UPD has been described in a single study (Gillessen-Kaesbach et al. 1995). In contrast, males with UPD have been found to be shorter at birth and to be depending on a shorter course of gavage feeding than babies with deletion (Mitchell et al. 1996). An interesting finding, however, is an increased age of the mothers of babies with UPD (Gunay-Aygun et al. 1997).
The differences in development are covering the issues of feeding difficulties, age of onset of food obsession and the age of the child when the syndrome was diagnosed. In general, the findings are heterogeneous. Some studies found no differences (Gunay-Aygun et al. 1997), whereas others found that girls with UPD had shorter periods of augmented feeding and later onset of hyperphagia and behaviour problems than individuals with deletion (Mitchell et al. 1996).

Of the physical differences of interest described between the genotypes, are that patients with UPD are less “fair” compared to their families and their faces are less likely to have the characteristic features compared to individuals with deletion. Children with deletion have also more frequently eye problems. Moreover, skin picking and nail biting seems not to be so pronounced by the UPD genotype. This could be related to the fact that fewer individuals with UPD were found to have increased pain threshold (Cassidy et al. 1997; Whittington and Holland 2004d), Table 3.

Compared to PWS caused by deletion, individuals with UPD were not found to overeat, hoard or be withdrawn to the same extend as their counterparts. Individuals with deletion were also found to be more affected by mood swings, lying, stealing and in general to have a more violent behaviour. Never the less, individuals with UPD have a high risk of developing psychosis in adult life (Boer et al. 2002). The large and often cited Cambridge study found, that all adults in their cohort with UPD suffered from major psychiatric illness (Whittington and Holland 2004d).

Previous literature confirms the many anecdotal reports that let know about individuals with PWS who are exceptional good at solving jigsaw puzzles. Especially persons with deletion are found to have this extraordinary enjoyment and skill (Dyakens 2002; Whittington and Holland 2004d), Table 3.

In conclusion, previous studies on phenotypic characteristics on the major different genotypes describe minor differences between UPD and deletion, where PWS individuals due to UPD in general seem to have the milder phenotype. However, until recently the clinical series were not based on skilful genetic investigations, and the prevalence of UPD in different studies varies accordingly. Although the number of affected individuals in recent
studies are relatively large, the number of the less often genotypes are few. Thus, the series might be biased or subjected to type 2 errors.

### Table 3. Significant differences between PWS, Deletion and UPD, (Whittington and Holland 2004d).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subjects</th>
<th>Deletion</th>
<th>UPD</th>
<th>Significance</th>
</tr>
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<tbody>
<tr>
<td>Possessiveness</td>
<td>All</td>
<td>33/49</td>
<td>24/26</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>17/30</td>
<td>11/13</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>16/19</td>
<td>13/13</td>
<td>ns</td>
</tr>
<tr>
<td>Sleep Apnoea</td>
<td>All</td>
<td>6/49</td>
<td>10/26</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>6/30</td>
<td>5/13</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>0/19</td>
<td>5/13</td>
<td>ns</td>
</tr>
<tr>
<td>Eye Problems</td>
<td>All</td>
<td>42/48</td>
<td>17/25</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Adults</td>
<td>28/30</td>
<td>11/12</td>
<td>ns</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td>14/18</td>
<td>6/13</td>
<td>0.01</td>
</tr>
<tr>
<td>High Pain Threshold</td>
<td>All</td>
<td>40/45</td>
<td>21/22</td>
<td>ns</td>
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<tr>
<td></td>
<td>Adults</td>
<td>27/27</td>
<td>11/11</td>
<td>ns</td>
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<td>Temperature Regulation</td>
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<td>16/23</td>
<td>ns</td>
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*Footnote: The Table shows the symptom distribution between the two genotypes of PWS. For example, for sleep apnoea: Of the 49 subjects with deletion, 6 had sleep apnoea (all adults), compared with 10 out of 26 with UPD. This difference was significant, P< 0.01.*

### 1.7 Cognition

Cognition describes the mental processes that transform the information we take in through our senses. It reflects aspects of how people perceive, learn, store, remember, and retrieve information; in general how humans deal with what they perceive, think and learn. Cognition is thought to be a combination of a general ability and a variety of specific abilities. In the not learning disabled population, general ability is influenced by both a genetic and an environmental component. The genetic inheritance, which is estimated to be responsible for
approximately 50-80 percent of the variance, is made up by a large number of genes (Falconer 1981). At the biological level, the brain is believed to provide the mind with neural mechanisms to be used as tools to build the functions of the mind. This means for instance, the ability to control and maintain attention and spatial orientation. The higher abstraction level attempts to characterize the mental functions themselves, which include the way information is perceived and held in the short time memory, processed in the working memory and kept in the long time memory (Hunt 2005).

Memory is one of the most important aspects of human cognition. Cognition is also concerned with higher levels of thinking as for instance how people understand causation, solve logical and mathematical problems (Hunt 2005), conduct a conversation and choose between alternative ways to act and react.

Obviously, a single over- or under expressed gene can have far-reaching and fatal consequences in a developing brain and subsequently for the whole person’s cognition.

1.7.1 Cognition in PWS

Because of the presumed failure of expression of a single or several genes, which results in an abnormal brain development, individuals with PWS are recognized as cognitive, emotional and social developmental impaired (Whittington and Holland 2004b). Therefore, PWS is associated with early developmental delay and learning difficulties (Table 1).

The literature on cognitive functioning, attainment and achievement of individuals with PWS is however, heterogeneous, with the same methodological limitations as previously mentioned. Again, these drawbacks might explain the discrepancies and contradictions in the different studies.

Some individuals seem apparently cognitive well functioning. This is mainly due to their mastery of a rich vocabulary and an advanced level of conversational skills. In common with other individuals with learning difficulties, the individuals with PWS are handling and managing concrete concepts better than abstracts (Whittington and Holland 2004b). The literature and anecdotes describe subjects with PWS as rigid and having difficulties with generalizing. Most of them, for instance have problems with the chronological placement in and the concept of passage of time. Their emotional and social impairment is illustrated by
the fact that caregivers declare that individuals with PWS have great difficulties in reading the emotional feelings of their surroundings. In cases where the emotional state is exaggerated or explicit visible, configured in either smiles or tears, it is more due to be understood (Whittington and Holland 2004b).

In the literature individuals with PWS have been variously described as having usually mild to moderate mental retardation, normal intelligence in a significant number of cases, learning disabilities, specific learning disabilities, characteristic cognitive weaknesses, good reading skills or weakness in arithmetic skills (Whittington et al. 2004b). Thus, individuals with PWS are generally described to fall within the range of mild intellectual impairment. The IQ of the individuals is usually described being within the 50-70 or 50-85 ranges. As many as approximately one-quarter of subjects with PWS have however, an IQ higher than 70 and approximately one-fifth even higher than 85. Never the less, they depict typical indications of having learning difficulties (Curfs et al. 1991;Curfs and Fryns 1992). Some extremes are mentioned at either end of the scale as for instance individuals having IQs below 40 or above 100. As to the first mentioned, these individuals might have suffered some kind of neurological damage in addition to having PWS. This could be explained by the fact that there are an unusually high percentage of babies with PWS who are delivered during abnormal conditions (Whittington et al. 2004b).

At the other end, few individuals with PWS have been found to have an IQ above 100. However, despite their elevated scores, their cognitive deficits were still apparent displaying the impression of the subject being mildly retarded (Sulzbacher et al. 1981;Whittington et al. 2004b).

In general the IQ distribution of the PWS population appears to be normal distributed, however shifted downwards by approximately 40 points compared to the general and normal population. In addition to this general lowering, the literature delineates that the subjects exhibit systematic areas of weakness. This means that the individuals have as well global as specific learning disabilities (Whittington et al. 2004a).

Within the population of PWS, cognitive similarities and differences have been described. Today it is generally accepted that the auditory modality in the group is more affected than the visual, which means that the individuals perform relatively better on visual-spatial tasks
They have deficits in sequential processing compared to simultaneous processing (Dykens et al. 1992; Warren and Hunt 1981), resulting in problems with tasks that require sequential operations as a lot of mental, academic and practical daily life do. As an example could be listed problems with following any kind of time schedule which normal life is full of.

On the positive side, individuals with PWS have a relative strength in solving simultaneous problems that require spatial-perceptual organisation and especially they are well performing on quests that require attention to visual detail and visual-motor coordination. (Curfs et al. 1991; Dykens et al. 1992; Gabel et al. 1986). Current literature describes that although subjects with PWS have intellectual disabilities and related adaptive behaviour deficits, they actually have relative strengths in self-help skills (Holm 1981; Thompson et al. 1996). The visual detail and visual-motor coordination skills might to a certain degree explain why some individuals perform exceptional well on jigsaw puzzle solving (Dykens 2002).

Previous studies reveal that the individuals suffer from a week short-term memory (State MW and Dykens 2000; Stauder et al. 2002). Academically, the listed restraints result in poor performance, especially within the area of mathematical operations (Bertella et al. 2005; Whittington et al. 2004b). Reading, decoding and comprehension, might exceed their arithmetic skills (State MW and Dykens 2000). Underachievement, defined as the difference between the score predicted from full-scale IQ and the actual academic achievement, has been found in the areas of reading, spelling and arithmetic (Whittington et al. 2004a). This underachievement has been found to correlate positively with the percentage of time in education spent in specialized schools. A probable explanation for this surprising finding might be that the priority in special schools often is placed on teaching of more practical coping skills. The emphasis of these schools often is placed on managing personal needs, getting along with domestic tasks and getting socialised into community and society rules. A positive correlation has also been described between underachievement in reading and BMI. This correlation is found in as well the individuals with PWS as in the individuals with learning disabilities (Whittington et al. 2004a).
1.7.2 Cognitive Differences across the Genetic Subgroups

The genotype of PWS is thought to have an important effect on the cognitive phenotype. The divergent cognitive profiles and differences are presumed to be due to different genetic influences on brain development (Whittington et al. 2004b). As to the above mentioned underachievement, it is found to vary by academic domain. The individuals with disomy are found to have a better reading skill, which was illustrated by the fact that, on average, they did not show underachievement in reading. Additional findings revealed that the differences in mean underachievement between the individuals having deletion and those with disomies were most pronounced in reading, slightly less in spelling and very little in arithmetic (Whittington et al. 2004a). Individuals with disomy are also described as having better verbal abilities, as for instance in vocabulary but impaired coding ability, which means reduced speed (Whittington et al. 2004b).

This finding is confirmed by studies showing that individuals with UPD have higher verbal IQ compared to persons with PWS due to deletions. Even so, no significant differences were found between the two subgroups neither on full scale IQ nor on Performance IQ. The literature reveals that, although individuals with UPD scored significantly higher on the verbal subtests, they did not achieve higher on reading or in other academic measures (Roof et al. 2000). An explanation could be found in the anecdotes that describe how well children with PWS due to UPD are at imitating both voices and personalities. Their previously mentioned, apparently high level of advanced vocabulary and conversational skills might raise equivalent expectations, which they cognitively find difficult to match (Whittington and Holland 2004b).

The unexpected lower performance by PWS with UPD might furthermore be related to a reduced capacity to discriminate forms that require stereoscopic vision (Roof et al. 1999). Thus, they perform poorer on visual organisation and spatial tasks (Fox et al. 1999). This finding is also consistent with studies revealing subjects with UPD to perform poorly on jigsaw puzzle tasks, compared to individuals with PWS due to deletion.

Some individuals with deletion were found to have strong visual-spatial skills and jigsaw puzzle skills that even were superior to those of non-intellectually impaired children at the same age (Dykens 2002). This exceptional performance on jigsaw puzzle could be explained
by extended prior practice due to the previously described passion for compulsive and repetitive behaviour. It is however, theorized that the initial interest in puzzle solving among the individuals with deletion might derive from a natural relative ability in visual-spatial tasks (Whittington et al. 2004b).
2. Memory

Memory is general in connected to a variety of different external, as well as internal mental processes. Throughout the history of psychology, there has been a lively debate of how to understand and depict the concept of memory. Probably because memory is closely related to the processes activated in learning, the topic has been of great interest in the field of cognitive psychology for more than a century. Memory was actively investigated in the early experimental, German laboratories of Wilhelm Wundt, Hermann Ebbinghaus and Georg Elias Müller (Saugstad 2001). As a process, it refers to dynamic mechanisms or phases which in the literature are referred to as encoding, maintenance or storage and retrieval of information. During encoding the sensory data gained is transformed into a certain kind of mental representation. In storage the encoded material is kept in memory and during retrieval the stored information is used (Baddeley 1998a).

Equivalent with the varieties of information processing models depicting and detailing the way the human cognitive processes and the mind works (Atkinson and Shiffrin 1968), also memory has been described and interpret in different ways, according to the changing psychological viewpoints, philosophy and approaches (Saugstad 2001). One question raised has been whether memory was to be considered as one entity or whether it was to be understood as different coordinative subunits (Baddeley 1992).

Within the latest decades, the connectionist model has gained terrain. According to that, information is stored in multiple locations throughout the brain forming networks of connections, comparable to that of a computer network. Based upon the connectionist model there is no such thing as an isolated memory “section” in the brain since one memory is connected to many others. The brain is regarded as a huge computer with a lot of memories which all are unified and interrelated (McLelland and Rumelhart 1986).

The traditional view of memory, however, is built on the assumption that human memory can be divided into a number of structural separate systems or stores through which information is transferred (Atkinson and Shiffrin 1968). This multi-store model of information processing has also been called the “boxes-in-the-head” approach or the “stage”
model since it compares information processing with the serializing of processing stages that takes place in computers (Krause et al. 2003).

During the years, the original concept has been elaborated; however the core idea has remained the same: Information is thought to be stored in three locations which are called the “sensory register”, the “short-term store” and the “long-term store”. The sensory register, the first compartment, stores information gathered through the five senses for only a few seconds. The second compartment, the short-term store (STS) or the short term memory (STM) or working memory (WM) (Baddeley 1986), is also a temporary storage which has limited capacity (Miller 1994). In order to remember the information in the STM, it is necessary either to rehearse or chunk it. The more effectively material is either rehearsed and/or chunked; the more likely is it to be transferred to and well stored in the long term memory.

In contrast to the former stores, long term memory (LTM) has unlimited storage and capacity time. This entity is presumed to be complex and to take many forms. Since the early 1980\textsuperscript{th}, the literature has suggested LTM to be divided into “episodic memory”, “semantic memory” and “procedural memory” (Tulving 1985). While these three memories differ in context and function, they are often connected. As in the case with short-term memory, rehearsal helps us to remember information stored in LTM. Elaboration of a theme in the sense of linking new information to something that is already manifested in LTM is another important strategy. The elaboration process relates the new information to the already existing and makes it all more coherent, meaningful and memorable. These strategies seem to be positively correlated with reading performance (Sturrock and May 2005).

2.1 Working Memory

Especially within the last two decades, the concept of working memory has been of growing interest and is today considered to be one of the trendiest and most discussed topics in cognitive psychology and the emerging field of cognitive neuroscience (Miyake and Shah 2004a). Working memory is considered a theoretical construct that refers to the mechanism in the brain, which keeps task-relevant information active, while it is processed during a certain cognitive performance. The term is used in different senses within the different fields
of research, and it has been referred to by different metaphors. Thus, there is some confusion about what the term actually covers and what it refers to. To the complexity adds that the literature seldom has made a distinction between working memory and short-term memory (Miyake and Shah 2004a).

Similar to the concept of human memory, different theories and models reflecting the nature, structure and functions of working memory exist side by side; the concept has been approached from many different angles and levels of descriptions. In an attempt to clear this rather “muddy water”, a common distinction has been drawn between researchers emphasizing working memory to be a unitary construct, the devotees of the so-called “domain general models”, versus researchers fractionated in the opposite camp depicting working memory to be consisting of multiple separate subsystems, the so-called “domain specific models” (Baddeley 1992).

This structural disagreement has an interesting historical parallel in the area of intelligence, where the early psychometric theory, represented by Spearman in 1904 argued, that one “general” intelligence, the “g” factor was the one and only source in all intellectual performance (Mentioned by Saugstad, (Saugstad 2001)). The diametric opposite view upon intelligence was presented by Guilford in the late 60th with his “Structure of Intellect” cube, listing as many as 120 different intelligences (Sattler 2001).

Because the multiplicity and diversity within labelling and modelling made comparison and fruitful scientific discussions among researchers in the working memory field almost impossible, an attempt was made to unite the seemingly incompatible and diverse theoretical claims and points of view. The ultimate aim was to seek a broad but unified theory and find agreement upon an operational definition of working memory (Miyake and Shah 2004b).

In addition to the above mentioned distinction between models, seven theoretical questions all touching central, highly debated and important issues in working memory, were formulated and distributed among ten of the leading international capacities in the field, for review see (Miyake and Shah 2004a).

The working memory models and concepts compared in the up-to-date review were all well-established and representing the current research within the field (Miyake and Shah 2004a). Despite the obvious and significant differences in theoretical standpoint, an emerging general
consensus actually appeared on six commonly discussed themes. The essence of this emerging agreement will briefly be referred below, because it is assumed to be the current “state of the art” of consensus on the topic (Miyake and Shah 2004b).

The first issue concerned whether working memory should be considered a structurally separate box or place in the mind or the brain. An agreement was reached that working memory could not any longer be considered as a separate unit or a structural separate box where a limited amount of information can be stored. Various areas of the brain work dynamically together at a complex neurobiological level, in order to contribute to the working memory process. Therefore the expression “to hold something in memory” obviously is misleading because techniques for studying the function and biology of the brain have visualised that a specific place does not exist.

Furthermore consensus was established upon the conviction that the role of working memory is much more complex, than previous believed. The working part of the word should be highlighted, because working memory is meant for working; it is much more than just a temporary memory or memorizing device, since it has a huge capacity and flexibility. It is closely intertwined with high level cognitive tasks as for instance problem solving, language processing, discourse comprehension and visuospatial thinking.

In general, there are many differences in research focus and definition. This might to some degree explain the disagreement between the researchers standing up for either the more unitary or the non-unitary nature of working memory.

Diving beyond this seemingly fractioning of all models, there is limited support for a completely unitary view of working memory. Most researchers believe, some way or the other, in domain-specific codes or representations, but they disagree on the subject of how these subsystems can be characterized and categorized. The point of discussion is really about, whether there are few or many subsystems. The models also differ in their description of the sources of domain-specificity effects. Last, but not least, the models represent a variety of subsystems disagreement among the types of distinctions, on which the division has been made (Miyake and Shah 2004b).

Concerning the nature of working memory limitations, all contributors agreed that no single, all-compassing capacity-limiting factor seems to exist. On the contrary; - a long vide ranging
variety of sources of limitations were listed by the representatives of the different models. The range of limitations could be classified into headings concerning whether they are universal in nature or vary across individuals, whether they are emergent or inherited and whether they are permanent or change over time (for review see (Miyake and Shah 2004b)).

Although there was, as above mentioned agreement that working memory is closely intertwined with high level cognitive tasks and plays an important role in solving complex cognitive challenges, the researchers displayed diversity coming to terms of how to define “complex cognitive tasks”. In general a consensus was reached upon the concept that a complex cognitive task is characterized by a task kept under cognitive control and involving several steps or stages of operations. In addition, the task has to involve several components of the working memory and by means of a certain speed require access to large amounts of information.

Much dual-task performance, which means complex cognition tasks requiring coordination of several different components of the subcomponents of working memory (Baddeley and Logie 2004), are today primarily studied in laboratories and under artificial circumstances. However, there seems to be a general agreement of the credibility of conducting studies on working memory in the challenging context of the real world.

Finally, there is emerging consensus acknowledging that information and proficiency already stored in LTM play an important part of current working memory performance - this despite the complexity of the task.

In an attempt to synthesize both the contributor’s individual definitions of working memory and the above listed issues of general consensus, the following all-encompassing working definition was proposed by A. Miyake and P. Shah (Miyake and Shah 2004b):

*Working memory is in those mechanisms or processes that are involved in the control, regulation, and active maintenance of task-relevant information in the service of complex cognition, including novel as well as familiar, skilled tasks. It consists of a set of processes and mechanisms and is not a fixed “place” or “box” in the cognitive architecture. It is not a completely unitary system in the sense that it involves multiple representational codes and/or different subsystems. Its capacity limits reflects multiple factors and may even be an emergent property of the multiple processes and mechanisms involved. Working memory is*
closely linked to LTM, and its contents consist primarily of current activated LTM representations that are closely linked to activated retrieval cues and, hence, can be quickly reactivated.

2.2 The Concept of Working Memory according to Baddeley

Alan D. Baddeley has actively been researching within the working memory field for approximately 25 years and in 1986 he developed a model which has become highly influential (Baddeley 1986). In collaboration with colleagues his original concept, however, has been reviewed and elaborated several times during the last decades (Baddeley and Hitch 1974; Baddeley and Logie 2004). Because it probably is the single most influential current view of working memory not only of the above mentioned selection of ten alternative models but in general, it will be introduced separately.

Furthermore, it will be given special attention, as it is the intention of this thesis to relate the pilot study to the newest version of the model (Baddeley 2000), and particularly to the visual part of the working memory.

The Baddeley and Hitch model divided working memory into a system composed of multiple components consisting of the central executive, the phonological loop and the visuospatial sketchpad. A more recent improvement to the model is the episodic buffer (Baddeley 2000).

The central executive element (CE) is the mechanism for controlling processes and distributing resources in working memory. It has been explained as an “attentional control system”, operating in conjunction with two parts, regarded as slave systems: The phonological loop and the visuospatial sketchpad. CE is thought to be responsible for controlling the encoding and retrieval strategies and “dual-task” coordination, which means that two tasks are being carried out simultaneously. Furthermore, the CE has been suggested to be responsible for the focusing, dividing and switching of attention (Baddeley 2002). In itself has no storing capacity (Baddeley and Logie 2004; Baddeley 2006).

The first slave system, the phonological loop, was the first and still seems to be the most studied component of the multicomponent model. It is domain specific as it is specialized in temporary storage of phonologically based material. It consists of two main components; the
phonological store and the articulatory control process. The first mentioned is a passive memory store that can retain speech-based information for a short period. Unless actively rehearsed, the traces within the store are assumed to fade and decay within approximately two seconds, after which they are no longer usable.

The articulatory control process is also responsible for two different functions. First, it translates the visual presented information into a speech-based code and secondly, it stores it in the phonological store. Adequate memory performance is therefore cooperation between functional storage, as well as rehearsal (Baddeley and Logie 2004). The rehearsal process is assumed to involve aspects of both speech perception as well as expression. Not surprisingly, the phonological loop is regarded to have influence on long-term phonological learning and is suggested to play an important role in the development of language in children (Baddeley et al. 1998).

The second slave system, the visuospatial sketchpad, is also domain specific as it is considered being specialized and responsible for visuospatial information in general. It is assumed to be apt to temporarily maintaining and manipulating visuospatial material in memory; a process that is considered crucial for performing a range of cognitive tasks. Similar to the phonological loop, the visuospatial sketchpad is suggested fractionated into a passive visual cache and an active spatially based rehearsal system called the inner scribe (Logie 1995). Different codes are suggested existing within this sketchpad, which might be responsible for the visual component being separated from its spatial counterpart (Baddeley and Logie 2004).

The rehearsal mechanisms related to the visuospatial sketchpad are challenging and less clear compared to the rehearsal process of the phonological loop. It is however suggested, that the spatial component of the system, the inner scribe, should be regarded as the basic mechanism for rehearsal (Logie 1995). Furthermore, it might be closer related to attention and preparation for action. Moreover, aspects of image generation are thought to support visual maintenance (Logie 1995). In general, the visuospatial sketchpad it is thought to play an important role in locating an object and the information regarding its visual appearance (Baddeley 1998b). In addition, both subsystems are considered involved with representation and planning of movements.
The visual and spatial components of the working memory seem to be linked, but not synonymous with the visual imagery system. This system is considered integrating visual information from various sources, including long-term memory. Both, imagery and visuospatial memory tasks are considered to involve long-term knowledge in connection with information retrieved from sensory receptors (Baddeley and Logie 2004).

In summary, the visuospatial sketchpad combines the visual and spatial information in memory as provided by sensory input, with long-term memory, to form an integrated memory store, consisting of the visual appearance, as well as the location of objects (Baddeley 1998b).

In order to explain how the visual as well as the verbal input from the two slave systems are bound together during encoding and thereby improving recall ability, the episodic buffer was introduced in the model of working memory. The episodic buffer is thought to function as a “back-up-store” capable of supporting serial recall, and presumably integrating phonological, visual and possibly other types of information ((Baddeley 2000), page 419). Furthermore, it is suggested to be capable of combining information stored in LTM with information from the visuospatial sketchpad and the phonological loop subsystems (Baddeley 2002).

2.3 Aim of the Study

Based on the Norwegian population of adults with clinical PWS, this study was based on individuals with a genetically verified diagnosis included in the Norwegian part of the Nordic Prader-Willi study. The Nordic study is a prospective randomized, controlled study with the purpose to investigate the effect of growth hormone treatment on body composition and cognitive function in adults with PWS (approved by the Regional Ethical Committee, 2004).

By means of a computer based cognitive test (CogState), the purpose of the present pilot study is, on a cross-sectional basis, to analyse aspects of the working memory in the participating adults.

The majority of the existing literature on PWS is dealing with the medical and genetic aspects of the syndrome. The literature describing cognition and the diversity within the
intellectual functioning of the individuals with PWS is rather sparse. Thus, the purpose of this thesis is to relate the findings of the pilot study to existing literature concentrating on cognitional aspects of the PWS syndrome, thereby enlarging the present body of knowledge.

This cross-sectional analysis is regarded as a pilot project within the Norwegian part of the Nordic Prader-Willi study. Achievements within elements of working memory are by means of CogState examined in the individuals.

The hypothesis of the study is that the effect of the impairment of cognitive function in adults with genetically verified PWS should not result in a significantly lowered performance in the tasks measuring and capturing areas of their cognitive strength (attention to visual details and visual motor coordination), when compared to a genetic not impaired population.

This study furthermore explores whether performance is influenced by anthropometric data (age, sex, and BMI) and previous treatment with growth hormone.

Moreover, the thesis will relate the results of the pilot study to reflections concerning aspects of life long learning.
3. Material and Methods

3.1 Cognitive Tests

Cognitive tests are used to measure the ability of a person to perform on a task from which assumptions and inference can be drawn about their cognitive function. They are assessments of the cognitive capacities and designed to capture the aptitude of either limited domains or broader aspect of cognition, according to their theoretical belief of how intelligence is to be defined. The purpose of making use of cognitive tests is most often to get an overview of the cognitive capability of the person at the very moment and under the actual conditions during which the test has been administered. Simplistic, one could compare it with a “here and now” picture of the tested persons cognitive potentials pictured by means of a certain tool; the test battery.

A variety of cognitive tests have been invented during the last century. The range of the tests reflects the focus intelligence and cognition has been given. The assortment includes a broad spectrum of analysis measuring on group or an individual basis. Psychometric, predicative, diagnostic, and achievement tests are just a few to be mentioned.

Some of the cognitive tests used today, are revised versions of tests which can be tracked decades back, where “paper-and-pencil” were the most important tools in conducting the test.

By the general and widespread use of computers during the past decades, computerized testing has quickly emerged in the testing field. There are obviously pros and cons connected to the use of this newest approach in conducting a test. Its spokesmen nevertheless emphasize, that computerized testing offers the most precise standardization and accurate recordings. The electronic capture and processing of data minimize human errors and the electronic administration of results reduces the sources of response bias.
3.2 CogState

In this present pilot study, we have used the commercial available CogState test-battery. The test was invented by a research team at the School of Psychological Science at LaTrobe University, Melbourne, Australia (http://www.CogState.com). The test battery and the company, carrying the same name, was founded 1999 and was elaborated in cooperation between industry and academic partners. This fusion of economic and scientific support and interests is still the pivot of the concept.

It is important to emphasize that CogState does not measure intelligence. All tasks within the battery are adaptations of standard neuropsychological and experimental psychological tests. The test measures a range of cognitive functions, such as reaction time, attention, visual- and long-term memory and learning, as well as planning and problem solving; all important aspects of the individual’s learning potentials. Because of its randomly interval and stimuli presentation the test has no learning effect (Mollica et al. 2004), and is therefore especially convenient for longitudinal studies like the Nordic Prader-Willi study. The changes in cognition are usually determined by means of a test-retest procedure; comparing the tested person with his or her own “baseline” level of performance. However, normative data do exist, making cross-sectional evaluations possible. As the present thesis is a cross-sectional pilot study of the above described longitudinal placebo-controlled trial, CogState was found to be useful. The battery has proven ability to detect both improvement and decline in cognition and is reckoned to be both a highly sensitive and reliable test, being able to detect even the slightest changes.

In general, it appears as a computer card game and it was originally created for use in aboriginal and less literal communities in Australia. Within its few years of existence the knowledge and use of it, however, has expanded. Apart from Australia it is now distributed worldwide from offices in the UK, Japan, and USA. As part of the present study, the on-screen instructions for the Norwegian version was translated and elaborated by the author alongside with testing of the individuals.

The body of research and the publications that include or are based on CogState data is rapidly growing and includes at present approximately 50 publications in peer-reviewed journals. According to the reference list of publications, the test has been used to determine
even subtle effects of a variety of drugs, as well as the effects medical or surgical devices and interventions might have on cognition. Subtests of the battery have also been a tool in assessing cognitive conditions in different diseases and disorders, in settings corresponding to the present study.

3.3 The Concept of the Test

The test battery consists of a selection of “standard tests” but in reality any combination of tests can be requested, depending on the interest of the study or the research needs. As the intension of our longitudinal study was to measure the effect of growth hormone treatment on cognition in the Norwegian adult PWS population, specific criteria determined the selection of the test items chosen.

As mentioned, it is generally accepted that individuals with PWS are especially well performing on quests that require attention to visual detail and visual-motor coordination. Moreover, previous studies have shown that individuals with PWS suffer from a week short-term memory and that the auditory modality in the group is more affected than the visual (State MW and Dykens 2000;Stauder et al. 2002). Thus, the individuals are expected to perform relatively better on visual-spatial tasks (Conners et al. 2000;Curfs and Fryns 1992;Stauder et al. 2002). Our intension was to tap the area in which, according to the literature, they perform the best; which is meant to be quests that require attention to visual details and visual-motor coordination (Curfs and Fryns 1992;Dykens et al. 1992;Gabel et al. 1986).

To ensure that the test battery tapped the optimal function domain of the population, the subtests were thoroughly selected in corporation with the Norwegian Competence Centre for PWS; Frambu. This will be further described in the following paragraphs.

The chosen selection of tests required no longer than approximately 20-25 min. to complete. It consisted of eight tasks in form of card games that were presented on a green screen. In order to instruct the individuals, a written instruction was presented by a small animated cartoon card king indicating the responses required during that particular task.
In the beginning of each subtest, a grey keyboard resembling that of a computer keyboard appeared in the lower half of the computer screen and the cards associated and used for that particular task were presented in the upper half of the screen.

Participants were required to respond with two keys; the “D” key which indicated the left response, and the “K” key which indicated the right response. In case the person was left-handed the response keys were switched. Participants were then given an interactive demonstration of the task, and as soon as they demonstrated their awareness of the rules, the task and with it the measurement of their performance began. If it during the test became clear that the participants did not truly understand the principles, the performance was interrupted and a new demonstration was performed.

Before the practise test, all individuals performed demo-version of approximately 15 minutes, in order to familiarize them with the system and to give the participant an idea of the layout of the tests to follow.

After the demo version, the practice part of the test was completed. It was an unabridged copy of the following baseline test. When entering the baseline test the participants were both confident with the test and the test items.

All together the participants had roughly 40 minutes of practice before commencing the baseline test. The long practise time was of positive value because, as previously mentioned the test had no learning effect, because of the randomized presentation of cards and colours.

Total duration time of the test procedure was approximately an hour, depending of whether or not the participant needed a break between the practice and baseline test section.

3.4 The Selection of the Subtests used

In Appendix 1, a further description of the tests and normative data are presented. In the test “Detection-part a”, a card is presented laying face down in the middle of the display. After a delay and at random time intervals, the card will flip over and lay face up. The participant is asked to press the “K”-key (or D if left handed), the indication for “yes”, as soon as she notices the card flips.
There are 35 trials and the duration time is approximately two minutes. The primary outcome measure is speed of performance (Appendix 1). The test is referred to measure simple reaction time and speed of processing. It is also supposed to measure the psychomotor function of the individual tested.

The second presented subtest is called “Identification”. This task is similar to the above with the one exception that the participants are required to indicate the colour of the card with their response. They have to press either the “D” or the “K” – key depending of what colour the card has, that flips. After 25 correct responses or expiry of the time the test is over. This subtest approximately takes two minutes as well. The test is supposed to measure the visual attention and the primary outcome measure is speed of performance.

The “Prediction” or “Problem solving task” is the third in the row. This subtest consists of two similar tasks; the latter more challenging than the first. The principle is that the participant first has to “guess” a random presented sequence of four colours/cards by pressing either the “K” (for red) or the “D” (for black) key. After having revealed the sequence by trial and error, the subject should try to remember it, because for four additional times, he or she is asked about the sequence of cards/colours just learned. The second part of the task is following the same procedure with the only exception that the cards/colours to remember consist of a series of sixteen cards.

This task takes approximately five minutes, and the primary outcome measure is accuracy of performance. It is also supposed to measure the executive function of the individual tested. Unfortunately, this test so far has no normative data available (Appendix 1).

The fourth test is the “One back learning task” in which a single card is presented in the middle of the screen. When the card changes, which it does every 2nd second, the individual has to decide whether or not the latter presented card is identical with the previous presented. Again the test person has to indicate her respond by pressing the “K”, for “yes” or the “D”-key for “no”. This test consists of 28 trials.

The duration of the task is approximately two minutes, and the primary outcome measures are speed of performance and accuracy of performance. The test measures working memory of the individual tested.
In the “Monitoring task” five cards, situated in the middle of the screen, are presented face up. The row of cards is located in-between two horizontal lines. As the task begins, the cards start moving, “jiggling”, randomly up toward the upper and down toward the lower horizontal line. The person must keep an eye on each of the moving cards because they will touch the lines at different times. As soon as the participant notices that one or several cards touch the line(s), he or she must press the “yes” key (K/D). The touch will reverse the direction of the card and it will start to “jiggle” toward the centre of the horizontal lines again.

In this test the card will touch the line 44 times and the duration of the task is approximately two minutes. The test measures divided attention of the individual tested and the primary outcome is speed of performance.

The “One-card learning task” is the next subtest. One card is presented face down in the middle of the screen. At a certain time, and with an approximately interval of two seconds, the card will flip over. As soon as it lays face up the participant must indicate whether or not she has seen the card in this task before. After having responded by pressing either the “K” or the “D” key, the card will go to the pack.

56 cards are presented; some several times, some not at all. The challenge for the participant is to remember whether the card shown has been presented previously. This task takes 5 minutes, and the primary outcome measure is speed of performance and accuracy of performance. This task is supposed to measure the visual memory.

The “Problem solving task”: delayed recall or “Prediction”: delayed recall is the as the name indicates a delayed recall of the long, sixteen number sequence of cards/colours presented and rehearsed four times: It was presented at the second part of task number three. In this delayed recall the participant is only once, without any further rehearsal, asked to recall the previous sequence.

This task takes less than a minute, and the primary outcome measure is accuracy of performance. This task is supposed to measure the subject’s long-term memory.

Last in the series of test is “Detection-part b”, which is a similar to the first subtest presented and described, see above. In this second part a total of 37 trials are presented. The
idea of presenting the same task twice, at either end of the test battery, is to measure whether or not the participants get exhausted by the procedure.

3.5 The Testing Procedure

In the attempt to minimize bias connected to the testing procedure, the content and the routines of the day the tests were carried out was kept as equivalent as possible for all participants. Depending on where and how remote the individuals live; they arrived at Frambu Competence Centre either on the same day or the day before the testing.

Prior to testing, all participants had been to a medical investigation at either of the collaborating hospitals. At 6 pm., when the participants had finished their dinner, the practice previous to the testing began.

For each participant, the author in collaboration with Competence Centre had elaborated an individual plan for the stay at Frambu. All participants were well instructed to the medical and cognitive program prior to arrival. We did not observe any frustrations or problems in relation to the testing procedure.

The fixed testing procedure and the individual plan were to ensure that the informant could be able to relax and feel as confident as possible. This was of greatest importance, because this particular population is extraordinary dependent on regularity and predictability in order to function at their best. Therefore the testing procedure was always carried out in the same room by the same test administrator.

The Competence Centre is a well known place to all the participants. They have all stayed at Frambu for shorter or longer periods in their childhood and adolescence years. Without any exceptions the individuals appeared relaxed and confident with the staff in charge during their present stay.

The thorough practicing before completing the subtests, the familiar surroundings as well as the positive atmosphere around the break out of the every-day routine were all endeavours to make the individuals feel confident and well-being and thus being able to concentrate on the tasks and perform their best.
Some of the subjects preferred to be alone with the author, others preferred to have either their personal caretaker or a well-known contact person at Frambu near them when tested.

As previously mentioned the first quarter of an hour the subject practiced on a short, demo-version of the test battery in which not all subtests were represented, but enough to give the participant an idea of the layout of the real tests to follow.

Total testing time was approximately an hour, depending of whether or not a small in-between break was needed or not.

### 3.6 Demographics

In the period August 2005 to October 2006 a total of 20 individuals with genetic verified PWS were investigated at Frambu and at Rikshospitalet/AHUS. One individual was in the very low cognitive function range. However, he was part of the main study and very motivated to perform the computer test too. Thus, we made two serious efforts to bring him through at least some of the test items. Although well willingly trying his best, his reaction time was far too long and we had to exclude him from the cognitive part of the study. Therefore, in total we present data on 19 subjects. The demographics of the population are presented in Table 4. The mean age of the population was 28.3 years (SD = 5.0) and there were 7 male subjects (36.8 %). According to the definition by WHO of overweight and obesity in normal subjects, 4 individuals had a normal weight, 3 were overweight and the rest obese (weight was missing on 4 subjects). The mean Body Mass Index (BMI) was 33.5 k/m$^2$ (SD = 10.6). The genetic background was deletion in most of the patients, only one individual had verified UPD.

As part of the main study, Polysomnography was accomplished in collaboration with The University Hospital in Akershus (AHUS). Four individuals were found to have severe sleep apnoea indicating treatment. These individuals started treatment before the cognitive analyses, and only one single individual was tested both before and after initiation of treatment.
Table 4. Demographics.

<table>
<thead>
<tr>
<th>Subject No</th>
<th>Subject ID</th>
<th>Born/age</th>
<th>Hand</th>
<th>Sex</th>
<th>Date of test</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N01</td>
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<td>Right</td>
<td>Female</td>
<td>26.10.2005</td>
</tr>
<tr>
<td>2</td>
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<td>1979/25.9</td>
<td>Right</td>
<td>Male</td>
<td>25.08.2005</td>
</tr>
<tr>
<td>3</td>
<td>N03</td>
<td>1985/20.8</td>
<td>Right</td>
<td>Female</td>
<td>25.08.2005</td>
</tr>
<tr>
<td>4</td>
<td>N06</td>
<td>1975/30.6</td>
<td>Right</td>
<td>Female</td>
<td>03.10.2005</td>
</tr>
<tr>
<td>5</td>
<td>N07</td>
<td>1979/27.1</td>
<td>Right</td>
<td>Male</td>
<td>15.06.2006</td>
</tr>
<tr>
<td>6</td>
<td>N09</td>
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<td>Right</td>
<td>Male</td>
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</tr>
<tr>
<td>7</td>
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<td>1968/37.0</td>
<td>Right</td>
<td>Male</td>
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<tr>
<td>8</td>
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<td>1970/36.0</td>
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</tr>
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<td>19</td>
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<td>1985/21.3</td>
<td>Right</td>
<td>Female</td>
<td>28.09.2006</td>
</tr>
</tbody>
</table>
3.7 Education, Independent Living and Work Placements

The current policy in Norway is to place children with special needs within the mainstream school system. Therefore most individuals in the described population have been integrated in mainstream schools, where they most often have attended special need units, special need groups or as fully integrated pupils in ordinary settings. Some of the oldest participants however, have in periods of their school life attended special schools as it was the official policy when they went to school. Whether they attended the mainstream school or were offered specialized education was depended of where in the country they lived and which schools were available.

All participants had attended some variant of mainstream school education for at least 12 years and had finished primary, secondary and secondary high school. Three of the individuals had additionally joined a folk high school. Two subjects are still going to classes at the secondary high school level in their leisure time.

As expected in an adult population, all but one of the subjects lives on their own in different versions of residential housing. All have approximately two personal guardians who help them with personal necessities and handling of the economy. They assist them in daily engagements and in keeping appointments and timetables. In collaboration with the individuals, municipal employees help with their cookery, shopping, cleaning and washing. In all aspects, the aim and officinal policy of the country is to promote a living for the individual which is as close to normal as possible - securing the quality of an independent life.

Being member of the work force is part of the normal life of an adult and adds quality to life. In Norway no individual with PWS is dependent of having a job for making the living, as all are financial taken care of by social welfare. Nevertheless all participants of the present study have a working place, offered either by the municipality or by the state, and they all have several years of work experience. Their working conditions as well as their occupation are especially arranged to meet their situation. The majority of the subjects hold some kind of sorting and packing, craft or office work; others help out as shop assistants. In general, all individuals work a full week with a mean of 24.5 working hours per week (range of 8.3-37.5 hours/week).
3.8 Statistics

As described in Appendix 1, the data in CogState are either given as the speed of performance in $\log_{10}$ of mSeconds or for accuracy of performance, as the arcsine proportion of correct answers. The individual and normative data are thus expected to be normally distributed. Moreover, individual Z-scores were calculated, which also would tend to a normal distribution within our population. It was therefore decided to use parametric statistics. As the normative data are divided in age groups of five years span beginning with the age of 25, we compared our youngest participants with the youngest normative data.

Individual results were transformed to Z-scores in relation to normative data by the formula: $Z = O - E / SD$; where $O$ is the observed result, $E$ is the expected value from the normative database (the mean of the age matched population) and $SD$ the standard deviation of the age matched group. The Mean, Median and SD of each subtest were then calculated. When comparing each subtest with normative data, the mean Z-score of the population was compared to $Z = 0$ by an independent $t$ test, where

$$t = \frac{\bar{Z} \times \sqrt{n}}{SD},$$

assuming in $H_0$ the mean Z value not to be different from $Z = 0$. The significance level was then found in a $t$-table, with $n-1$ degrees of freedom.

The further analyses within the population were based on dichotomising groups, either by sex or by the median value of the single subtest. The comparisons were made by $t$ test for independent data. In the paired situation (comparing Detection 1 and Detection 2), $t$ test for dependent data was used. When analysing variance in the time dependent items, an analysis of variance was performed a priori (Multivariate tests for repeated measures). If significant, $t$ test for dependent data was performed post priori. Relations between variables were tested by Pearson’s correlation analysis.

Statistical analyses were performed in SPSS version 13.0. All tests were performed two sided and the level of significance was set at $P < 0.05$.

All individuals gave informed consent prior to participating in the study. Special attention was paid to the fact, that the individual subject might not understand the consequence of the
informed consent. The consent was therefore approved by the closest family or the guardian. The protocol was approved by the local ethical committee.
4. **Results**

In general, the subjects were very motivated to participate in this part of the study. Almost all of them were comfortable with operating a computer, as most of them used computer programs in their leisure time at home. Thus, they had experience in playing several patience plays. Through prior practice and rehearsal before performing baseline data the subjects were familiar with the concept and layout of the cognitive test to be used in the study, and they all had positive association with computers and card games. With no exceptions participants performed the test procedures without problems.

The test is a computerised test installed on the local computer but analyzed by the server at CogState in Melbourne, Australia. Due to technical problems, some items are missing on subject no 7. Otherwise, the CogState data set is complete.

4.1 **Baseline Data Compared with Normative Values**

The baseline cognitive data derived from the CogState test are presented in Figure 1a and Figure 1b, where data are compared with the normative data presented in Appendix 1. Individual scores are given in Table 5. For all data presented, a positive Z-score for speed measures indicates a worse performance, while a negative Z-score a better performance and vice versa for accuracy measures (a positive Z-score a better performance). As seen from the Figures, the overall impression is that the PWS subjects had a markedly and significantly slower performance in the speed related items. Concerning accuracy, the scores were markedly and significantly lower than controls indicating a less accurate performance.
Table 5. Individual test results given as Z-scores compared to normative data (Appendix 1). For speed related performances, a positive Z-score indicates an impaired performance, for the accuracy related items (OCL/ACC and ONB/ACC) a negative Z-score indicates a worse than normal score. For abbreviations, see text.

<table>
<thead>
<tr>
<th>Individual Number</th>
<th>IDN z-score</th>
<th>MON z-score</th>
<th>OCL/ACC z-score</th>
<th>ONB z-score</th>
<th>ONB/ACC z-score</th>
<th>DET 1 z-score</th>
<th>DET 2 z-score</th>
</tr>
</thead>
<tbody>
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<td>03</td>
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<td>-0.334</td>
<td>-1.389</td>
<td>1.196</td>
<td>-11.840</td>
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<td>1.682</td>
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<tr>
<td>05</td>
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<td>-0.662</td>
<td>-3.011</td>
<td>1.905</td>
<td>2.372</td>
</tr>
</tbody>
</table>
4.1.1 Identification (IDN)

In the identification test, all subjects had a positive Z-score, indicating a slower performance compared to normality. The range of Z-scores was from 0.755 to 3.457 with a mean Z-score of 1.628 (SD = 0.887), meaning that the mean of the present population had a slower performance compared to the normative data of 1.6 SD. The difference from zero was highly significant (P < 0.001).

4.1.2 Monitoring (MON)

The speed of monitoring indicating divided attention is presented as the second task in Fig. 1a. As seen, most of the individuals had a positive Z-score, however two subjects had slightly negative values (-0.130 and -0.334, respectively). The mean Z-score was 1.718 with a SD of 1.625, indicating slower performance than normal individuals and thereby a decreased divided attention. The difference from Z = 0 was highly significant, P < 0.0001.

4.1.3 One Back Learning (ONB)

This test of working memory is presented in Fig. 1a as speed of performance and in Fig. 1b as accuracy of performance. The speed of performance was on a group basis significantly slower than normative values, with a mean Z-score of 0.916 (SD = 1.034), P = 0.001. As seen in the figure, the individuals did relatively better in this test with a mean performance within 1 SD below the normative values. Four of the individuals actually had a negative Z-score (from -0.063 to -1.039), thus performing better than the normative mean. The accuracy of performance was markedly below normative values (see Figure 1b). The range of the Z-scores was from -0.609 to -14.905. The mean Z-score was -7.204 (SD = 5.236) and highly significantly different from zero, P < 0.0001. There was no trend that the individuals with the best time of performance had a better accuracy.

4.1.4 Detection (DET 1 and DET 2)

This test of simple reaction time and thus psychomotor function and speed of processing is presented twice in the test procedure, at the beginning and at the end. As seen in Fig. 1a, all individuals had a positive Z-score at both tests with a mean Z-score of DET 1 of 1.972 (SD =
1.464) and of DET 2 of 1.963 (SD = 1.126). Both tests indicated significantly decreased psychomotor function, P < 0.0001. There was no significant difference between performance on DET 1 and DET 2. Moreover, DET 1 and DET 2 were highly significantly correlated. There was thereby no indication of exhaustion of the individuals from the beginning to the end of the test procedure (Figure 2).

4.1.5 One Card Learning (OCL)

This test measures visual memory and speed of performance. The results of the learning accuracy are presented in Figure 1b. The mean Z-score was -1.046 (SD = 0.919), which was significantly different from zero, P < 0.001. However, three of the individuals did demonstrate better performance than normal (Z-score range: 0.217 to 0.919).

4.1.6 Prediction (PRD)

We have not received normative data for prediction and could thereby not calculate Z-scores. On a group basis, the mean value of prediction was 2.996 Log_{10} mSeconds with a SD of 0.204. The accuracy was 0.756 (SD = 0.087) as the arcsine transformation of the proportion of correct responses.
Figure 1. Speed related tasks (Fig 1a – upper) and accuracy (Fig 1b - lower) of the CogState test presented as Z-scores in relation to normative data. For each task, the median, interquartile interval and total range is presented. Individual out-layers are indicated with a number referring to individual number in Table 4. * indicates significance levels, P < 0.001. For abbreviations, see text.
Figure 2. Correlation between the speed related tasks Detection 1 and Detection 2 of the CogState test presented as individual Z-scores. The correlation is highly statistical significant (P < 0.001). Approximately 60% of the variance in DET 2 is thus explained by the variation of DET 1 ($r^2$).

4.1.7 Relations between Subtests.

In order to analyse whether the results of the different items were related to psychomotor function as measured by DET 1 and DET 2, correlation analyses were performed. As seen in Figure 3, all subtests were significantly correlated to DET 1 except for OCL accuracy ($r = -0.393$, N = 18; P = 0.107). As to be expected, DET 1 was positively correlated to the speed related and negatively correlated to the accuracy related items.
**Figure 3 a and b.** Correlations between Detection 1 (DET 1) and the speed related tasks Identification (IDN) and Monitoring (MON). The different plots present individual Z-scores in relation to normative data.

**Footnote: Approximately 34% of the variance in the IDN task is explained by the variance in DET 1 ($r^2$)**

**Footnote: Approximately 41% of the variance in the MON task is explained by the variance in DET 1 ($r^2$)**
Figure 3 c and d. Correlations between the Detection 1 (DET 1) and the speed related task One Back learning (ONB) and the accuracy related ONB. The different plots present individual Z-scores in relation to normative data.

Footnote: Approximately 28% of the variance in the ONB task is explained by the variance in DET 1 ($r^2$)

Footnote: Approximately 23% of the variance in the ONB task is explained by the variance in DET 1 ($r^2$)
4.2 Within Group Differences

In order to study the potential within group differences, the PWS population was dichotomised according to sex (63.2% females), the median age (27.2 years), and median BMI (32.0 kg/m²). Moreover, as several children with PWS in Norway in recent years have been offered treatment with growth hormone (GH), we also looked whether any difference could be detected between our subjects in relation to previous treatment with growth hormone.

4.2.1 Cognitive Function in Relation to Sex

The difference in relation to sex for the Z-scores of speed and accuracy are presented in Fig. 4a and 4b. There were no significant differences between the sexes in speed of performance, as given in Fig. 4a. For accuracy parameters, however significant differences were demonstrated, as seen in Fig 4b. For One Card Learning accuracy, the mean Z-score for female individuals was -0.689 (SD = 0.920) compared to mean Z-score for males, Z = -1.761 (SD = 0.305), P = 0.014. This indicates that our female subjects had a better visual memory than males and with a mean score within one SD from normal. Female individuals had also a significantly better accuracy in the One Card Back Learning task, compared to males, indicating a better working memory. However, the mean Z-scores for both sexes were far below normal values, as the mean score for females was -5.066 (SD = 4.880) and for males -10.871 (SD = 3.711), P = 0.015. When prediction was related to sex the same trend was observed, however insignificant. The mean speed value of prediction was 2.933 Log₁₀ mSeconds (SD = 0.160) for women and 3.041 Log₁₀ mSeconds (SD = 0.264) for men, obvious without difference and statistical insignificant. Women had a slightly better prediction accuracy than men, with a mean accuracy score of 0.782 (SD = 0.061) versus 0.696 (SD = 0.104) as the arcsine transformation of the proportion of correct responses. This difference was of borderline significance, P = 0.08, Figure 5.
**Figure 4.** Speed related tasks (Fig 4a – upper) and accuracy (Fig 4b - lower) of the CogState test presented as Z-scores in relation to sex. For each task, the median, inter-quartile interval and total range is presented. Individual out-layers are indicated with a number referring to individual number in Table 4. * indicates significant differences between the groups. For abbreviations, see text.
Figure 5. Accuracy of prediction score in relation to sex. Data are presented as arcsine transformed accuracy score, where a higher score indicates a more accurate performance. For each task, the median, inter-quartile interval and total range is presented. Individual outliers are indicated with a number referring to individual number in Table 4.

4.2.2 Cognitive Function in Relation to Age

The median age of the population was 27.2 years. By dichotomizing the population by this age, we got 9 individuals below and 10 above the median value. As shown in Fig. 6a and 6b, there was no age dependency of any of the tasks performed. For example, in the One Card Back accuracy, the youngest age group had a mean Z-score of -8.861 (SD = 5.312) compared to older group with a mean Z-score of -5.731 (SD = 4.955). However, the difference between the Z-scores was not significant (P = 0.20). No differences in prediction between the age groups could be demonstrated, neither as speed of performance values or accuracy of prediction, data not shown.
Figure 6. Speed related tasks (Fig 6a – upper) and accuracy (Fig 6 - lower) of the CogState test presented as Z-scores in relation to age. For each task, the median, inter-quartile interval and total range is presented. Individual out-layers are indicated with a number referring to individual number in Table 4. For abbreviations, see text.
4.2.3 Cognitive Function in Relation to Body Mass Index

The population was divided into two groups in relation to the median BMI, which were 32.0 kg/m$^2$. As seen in Fig. 7a and 7b, there was no influence of BMI on the speed related performances. For accuracy however, the more obese subjects scored better in the One Card Learning task, indicating a better visual memory. The mean Z-score for the group with BMI > 32.0 kg/m$^2$ was -1.712 (SD = 0.511) versus Z = -0.800 (SD = 0.876) for the group with BMI < 32.0 kg/m$^2$, P = 0.042. Concerning prediction, the same trend was found. The more obese group had a slightly better prediction accuracy, with a mean prediction accuracy score of 0.784 (SD = 0.64) for the group with BMI > 32.0 kg/m$^2$ versus 0.721 (SD = 0.91) as the arcsine transformation of the proportion of correct responses. This difference was insignificant, (P = 0.16), data not shown. The mean speed value of prediction was without any difference between the two weight groups, data not shown.

4.2.4 Cognitive Function in Relation to Previous treatment with GH

A total of 8 individuals had previously been treated with growth hormone for shorter or longer periods. None of these had been treated during the least year before including in the study. As to be expected, this subgroup was younger (25.5 years) compared to the never treated group (30.7 years), P< 0.01. No differences between the two subgroups were observed in relation to sex distribution or BMI. As given in Fig. 8, the previous treated subjects scored better than the never treated in the speed related performances and the same trend was observed for prediction. The differences between the two groups in Z-scores were from 0.82 to 1.08 SD, however only statistical significant for Identification and One-Back Memory (P< 0.05 and P< 0.03 respectively). No differences for accuracy parameters were observed.

4.2.5 Variance between the Different Tasks

As outlined in 4.1.7 close correlations were observed between the task measuring psychomotor function and most of the other different items. In order to analyse the relationship between the different sub-analyses, multivariate analyses were performed by repeated measurements for the speed related tasks. The multivariate analysis the speed related tasks showed a significant difference between the tasks whether or not DET 2 was
included (if only DET 1 included, P = 0.023, F = 3.928). Thus, the a priory test showed a significant difference between the speed related items (Figure 1). The following t-test for dependent variables showed a significant better score (a Z-score closer to zero) for the task ONB compared to IDN (t = 3.259, P = 0.005, df 17), for ONB compared to MON (borderline significant, t = 2.053, P = 0.056, df 17) and compared to DET 1 (t = 2.983, P = 0.008, df 17). Thereby, we can conclude, that the individuals scored significantly better in the speed related performance ONB compared to the other tasks. For the two accuracy related items, the individuals scored significantly better in the OCL accuracy task (t = 5.369, df 17, P < 0.001), measuring visual memory, compared to ONB as clearly seen in Figure 1. This item was the only item not significantly correlated to DET 1.
Figure 7. Speed related tasks (Fig 7a – upper) and accuracy (Fig 7b - lower) of the CogState test presented as Z-scores in relation to BMI. For each task, the median, inter-quartile interval and total range is presented. Individual out-layers are indicated with a number referring to individual number in Table 4. * indicates significant differences between the groups. For abbreviations, see text.
Figure 8. Speed related tasks (Fig 8a – upper) and accuracy (Fig 8b - lower) of the CogState test presented as Z-scores in relation to previous treatment with GH. For each task, the median, inter-quartile interval and total range is presented. Individual out-layers are indicated with a number referring to individual number in Table 4. * indicates significant differences between the groups. For abbreviations, see text.
5. Discussion

The present study of genetically verified adult individuals with PWS showed significantly decreased elements of working memory compared to age matched, Australian normative data. In general, in the different subtests the PWS performing subjects had median scores within two standard deviations below the normal mean, however with great differences between the tests performed. Moreover, extensive inter-individual ranges were observed. Only in a few instances, an individual subject had a score better than the mean of the normative values.

The study also discovers that within the group of PWS subjects, females did significantly better than male participants in some of the items. When working memory was related to BMI, we found the more obese to have a slightly better ability of learning compared to the less obese. We could not demonstrate any effect of age in the results of the tests used. Moreover, no signs of exhaustion were demonstrated through the individual test situation, as the score of detection did not decrease from the beginning to the end of the test.

In this chapter the results of the study will be summarized and discussed. According to their relevance, the results are going to be discussed in relation to the four different kinds of validity elaborated and presented by Donald T. Campbell and his collaborator Thomas D. Cook (Kvernbekk 2002).

5.1 Validity in Relation to the Present Study

The aspect of validity is of greatest importance in all kinds of scientific research. Validity has to do with reality, truth and power in and of the findings, and conclusions drawn. Valid findings describe authentic and true facts, but even though the notion of truth has been enthusiastically discussed in the academic world since ancient time, it still is difficult to handle. It is important to keep the complexity of the world in mind when we in relation to science and results operate with grand concepts as validity, reality and truth. We have to keep in mind the scientific critics exemplified by Popper that “Science does not rest upon solid bedrock”, as referred by Kvernbekk (Kvernbekk 2002). In the apprehension of the impossibility of finding, the one and only truth and reality definitions, results and discussions
are meant to be understood in the paramount of the degree of truth; how close we have succeeded in reaching it. Knowledge and truth in the world of today is hardly expected also to be the truth in the future.

This pilot study is by design a cross-sectional descriptive study, and as already mentioned part of a longitudinal double-blind, randomized intervention study. In descriptive designs, the aim is to describe the “reality” as it is, by means of a “tool”. In addition to describing, these explanatory designs often try to find justification of why result findings are as found (Kleven 2002). This leads to the difficult question of causality. Because descriptive designs have no intervention and do not manipulate an independent variable, the design inevitably is weaker with respect to internal validity. This means problems with drawing conclusions of what has caused the results found. In an alternative effort to gain some degree of control, the researcher has to rely more heavily on the study design and alternative and often divergent ways of interpreting the findings. As a consequence of the descriptive design exhibiting little internal control, the statistical methods to confirm validity become an important aid for plausible explanations and interpretations of the results (Kleven 2002).

5.1.1 Aspects of Statistical Validity

In order to claim results to be statistically valid, the findings have to be significant and having a certain statistic power. If the results have statistic power the researcher more heavily can rely on the correctness of his findings. Statistically significant findings mean powerful and trustworthy findings. Well-known factors that decrease statistic power are for instance small and inhomogeneous samples and a low significance level. A fundamental prerequisite for getting trustworthy statistically valid findings is that the test used is reliable and has verified construct validity in order to keep random errors to a minimum (Lund 2002).

In this pilot study, we did not perform any a priory power calculations. When the statistical analyses were performed, comparing Norwegian individuals with PWS with Australian normative data, highly significant differences were found for all items investigated. Thus, we did not identify any potential type 2 errors. The risks for type 1 errors are given by the P-values, and in general at a very low level (P < 0.001) in this study. In this context, it is also a point that only exceptionally the individuals scored were better than the normative mean. This underscores the statistical result, that \( H_0 \) stating no difference between the two
populations was rejected. The parametric statistical methods used were based on normal distributions of data. The data presented were logarithmic or trigonometric transformed and moreover individual Z-scores were calculated ensuring normal distributions. Moreover, the data generated by the test battery have been shown not to be skewed, without range restriction and without floor and ceiling effects (Mollica et al. 2004).

5.1.2 Aspects of Construct Validity

Measures should be valid, which means they should capture the dimension of interest, as well as being reliable. This means that they should be steady and consistent from one administration to another. Good operational measurements are dependent of optimal construct validity. Construct validity is defined by means of how well the researcher has succeeded in establishing sufficient and correct operational measurements for the concepts being studied (Kleven 2002). It is considered to be of greatest importance to be aware of the challenges this validity represents. Especially caution has to be paid when generating truth of generalisation about higher order abstractions from the variables used in the study. Moreover, it is of great importance how the variables measured are anchored in a specific theory; what theoretically is supposed to be captured in the variable measured. The overarching theory and the empirical tested concepts are therefore closely related.

Besides striving for making each measurement as valid as possible, there are methods to improve construct validity and reliability and thereby minimize inaccuracy in the measurement and increase the reliability of the findings (Hjardemaal 2006; Kleven 2002).

Bias is distortion of measurements. When a test happens to measure irrelevant or only partly succeeds in confining the concept it claims to capture, the findings are biased in a systematic way. Random errors bias the findings in unsystematic ways. Measuring the same phenomenon several times offers the findings stability. Other ways of stabilizing measurements is to use multiple sources of evidence. Theory, methodological, information and researcher triangulation are ways to improve the equivalence of concepts being studied (Hjardemaal 2006).
To establish a chain of evidence in order to enable an external investigator to trace the research process in either direction is also considered improving validity (Hjardemaal 2006; Kleven 2002).

In the present study only one type of evidence was used to measure the concepts of elements of the working memory of the participants. Furthermore, the subjects did not repeat their performance, as the baseline test only was taken once.

Considering the concepts being studied, the CogState battery claims to assess the psychomotor, attention, long-term and visual memory as well as the executive functions of the participants tested. In an effort to enlighten eventual systematic bias of the study, research literature consulted indicated that CogState test has been applied in various experimental and clinical studies. In comparison with conventional cognitive tests, it was found to be even more reliable and furthermore just as sensitive (Collie et al. 2003; Silbert et al. 2004). This could indicate that the battery has a decent degree of construct validity and that the constructors have succeeded in establishing sufficient and correct operational measurements for the highly demanding and abstract concepts being studied. In other words, the battery seems to measure the concepts it certifies, indicating that the results are not influenced by systematic flaws.

The CogState battery has so far mostly been used and compared to cognitive tests detecting changes in psycho-motor as well as central nervous system functioning (Collie et al. 2003; Collie et al. 2006; Mollica et al. 2004; Silbert et al. 2004). For further improvement of reliability and implementation of the battery but, CogState should be analyzed and evaluated to more widely used neuropsychological tests, for example the well known Wechsler tests.

In an effort to meet the bias of random errors, the whole concept of the testing was kept as equal and rigid as possible. Thus, the administrator, the presentation, the practice, the comments and encouragements, the time of the day as well as external test surroundings were kept as constant as ever possible.

Further investigation revealed that the test is not constructed on the basis of one specific theory (M. Falleti, personal communication, July 6th, 2006). However, the splitting up of memory and working memory and the labelling used could indicate that the theory behind
the test is related to a variant of the “stage” model and Baddeley’s model of working memory, as discussed in details previously.

Studies have found that individuals with PWS are characterized by a weaker short term-memory or working memory compared to long-term memory (Dykens et al. 1992). According to memory discussion, it is, though, difficult to make a clear distinction between working memory and long-term memory, as the different areas of the brain work dynamically together at the neurological level in order to contribute to working memory performance (Miyake and Shah 2004b). Knowledge and skills already stored in the long-term memory also seem to play an important role in the current working memory performance despite the complexity of the task (Miyake and Shah 2004b).

Individuals with PWS are assumed to perform better on task that require visual processing compared to tasks that require auditory processing (Conners et al. 2000; Curfs et al. 1991; Dykens et al. 1992; Gabel et al. 1986). As presumed by Baddeley and Hitch and presented in their model of working memory, the first slave system, the phonological loop consists of two main components; the phonological store and the articulatory control process. The latter translates visual presented information into a speech based code before storing it in the phonological store (Baddeley and Logie 2004). With respect to their theory, it becomes difficult clearly to separate visual processing from the auditory modality. Some of the participants might have articulated and used inner speech and thereby they might have lowered their performance by making use of their in general lowered and impaired auditory modality. Others might to a certain degree have been able to rehearse and memorize the visual stimuli and thereby have improved their performance.

In spite of the fact that the task measuring visual memory (OCL) for cognitive well functioning individuals is extremely challenging, one have to keep in mind that the design of CogState is different from traditional tasks measuring visual memory (Logie 1995; Neath and Suprenant 2006). Individuals who either due practice or due to genetic advantage (Curfs et al. 1991; Dykens 2002; Whittington et al. 2004b; Whittington and Holland 2004d) are visually especially well performing and as a leisure activity often are enjoying card games, might have developed strategies for remembering features presented on playing cards. In accordance, the OCL item was the individuals performed significantly best.
Concerning the findings that subjects with PWS perform especially well on visual-spatial tasks (Conners et al. 2000; Curfs et al. 1991; Stauder et al. 2002), this task is not so easy to separate either. Paying respect to Baddeley and Logies Multi-Component model of working memory, the visuospatial sketchpad is fractioned into two components (Logie 1995) and thought to combine the visual and spatial information in memory with long-term memory. To isolate visual-spatial performance from general cognitive capability is however difficult, because the episodic buffer is suggested to be capable of combining information stored in LTM with information from visuospatial sketchpad and the phonological loop subsystems (Baddeley 2002).

5.1.3 Aspects of Internal Validity

Internal validity refers to the causal link between dependent and independent variables. Internal validity is de facto concerned with determining, whether the relationship between the program inputs and the measured or observed outcomes is causal or said in another way: Aspects of internal validity are striving to determine whether a program or an intervention a, is responsible for an outcome b (Kleven 2002).

Causality is of greatest importance and interest, therefore methodology literature has depicted a broad variety of threads to internal validity. However, causal relation has only to be given serious awareness and considerations in experimental as well as in quasi-experimental research. This indicates that the logic of cause and effect is inapplicable to descriptive and exploratory studies (Kleven 2002; Lund 2002).

According to previously mentioned literature, it is the failure of expression of either a single or several genes which assumingly are responsible for the features, inclusive the cognitive and early developmental delay associated with PWS (Whittington et al. 2004b). This genetic difference is also presumed responsible for the downward shift by approximately 40 IQ compared to the general population (Whittington et al. 2004a), as well as for the auditory modality of the group being more affected than the visual (Conners et al. 2000; Curfs et al. 1991; Stauder et al. 2002).

Therefore when speaking of causality in the present pilot study the question could be interesting as to whether the genetic difference in the population investigated might be due to
lowered performance in speed and accuracy when compared with the performance of the normative population.

Because the relative strengths of the population with PWS is simultaneous problem solving and especially on tasks that require attention to visual detail and visual-motor coordination (Curfs et al. 1991; Dykens et al. 1992; Gabel et al. 1986), the hypothesis of this study was that the effect of the above described genetic impairment should not result in significantly lowered performance in tasks that measured and captured their strengths, when compared with a genetic not impaired population.

Even though this hypothesis obviously was rejected, the causality in the study is far from evident. A third variable as for instance intelligence or other, spurious variables could be held responsible for the findings (Kleven 2002). This study did not explicitly control for the influence of intelligence primarily because no such data on beforehand were available. Intelligence and working memory however, are presumed to be closely related, which is the reason why an item of the Wechsler test batteries, *number repetition*, is considered to measure the working memory of the person tested. Only few of the participants but, had previously been fully cognitively assessed. Again it depended of where in the country they lived and which school they had attended.

To summarize it is extremely difficult to draw some finite and waterproof conclusions about causality in this descriptive, non-experimental study. Because of the many subtle and alternative factors which eventually may play an important role, the interpretations and conclusions of the cause and effect of the results have to be thoroughly discussed and kept modest (Kleven 2002).

### 5.1.4 Aspects of External Validity

External validity is concerned with the generalizability of the findings, whether the findings in the investigated sample are applicable to the whole population.

Investigating homogeneous groups is a way of keeping irrelevant variables under control. There is, however, often a trade off between internal and external validity. In other words; designs that do well on one dimension do not always do well on the other dimension. In
designing a study one therefore has to weigh the pros and the cons in relation to what is considered to be most appropriate in the actual situation (Kleven 2002).

Good external validity in a study implicates that the findings with a certain degree of probability are applicable and possible to generalise over and to other relevant situations, other individuals and aspects of time, in the general population they represent (Hjardemaal 2006; Lund 2002). If the aim is to secure good external validity the sample has to be representative in order to draw justifiable and statistically conclusions. The sample has in as many ways as possible to be representative for the general population it represents. As a realistic consequence, the sample should represent a certain degree of heterogeneity; securing that for instance not only one character is being investigated. On the other hand, the more inconsistent the findings are, the more uncertain it becomes to make generalizations.

There are different methods and ways to withdraw informants from the total population. The two basic ways are either to pick particular people for particular reasons; the so-called purposive sampling or allowing the laws of chance to determine who is participating; the so-called random sampling. The size of the sample is of importance to keep in mind; the larger the sample the more valid the generalization becomes (Hjardemaal 2006; Lund 2002).

The present study investigates a homogeneous group, because all participants in the sample have genetically verified PWS. Nevertheless, this does not implicate that the sample does not represent a certain degree of heterogeneity. This fact is clearly illustrated by the previously described demographic data of the individuals. The statistically conclusions drawn from the results confirm that the findings represent as well group homogeneity as well as within group heterogeneity (to be discussed in detail in the following chapters).

The way the sample was selected was a variant of purposive sampling. Actually, the sample very much assembled itself. The only population of interest in this study was adult with verified PWS living throughout Norway. Therefore, all potential subjects were contacted and invited to participate in the study. Several more individuals were invited than finally participating. Some were excluded from the study because the genetic diagnose could not be verified, and therefore they did not meet the criteria for participating. Others met the criteria but were cognitively found to function so poorly that they could not perform the test within the implemented time limits. A third group could not participate because they were stressed
by the conditions under which they lived - they lacked the organisation, predictability and supervision the population with PWS need so badly.

Nonetheless, the size of the sample is actually impressing, as it includes more than half of the adult population with clinical PWS living in Norway today (Landsforeningen for Prader-Willi syndrome 2005) and most probably the vast majority of individuals with genetically verifiable PWS. Thus, as a consequence of the thorough registration and the good contact the Competence Centre Frambu has with this population and the strict criteria delineated in the protocol for the longitudinal study, the external validity of this study is presumed to be good.

5.2 Perspectives of the Present Pilot Study

This study shows that most adults with PWS have attend mainstream schools with or without special need groups and/or units on primary, secondary and high school levels for approximately 12 years. Due to their age, some individuals have in periods attended special schools in accordance with previous Norwegian policy at the time. All participants in the study are living on their own, by means of caretakers and personal guardians, which organize and in all aspects help them to live an approximate close to normal life. They have all jobs in their neighbourhood which are matching their skills and, hopefully their interests. They work independently but are also part of a work team. Also their working hours are individually matched to their abilities. Most of the subjects work long hours and have an approximate normal work-week. Social assurance makes it possible for everyone to live an economically independent life, but additionally everybody earn their own money as their work is paid. The project “Inkluderende Arbeidsliv” has centres, “Trygdeetatens arbeidslivssentral”, where they give good advice to as well employees as employers for individually designing and matching skills and interests with jobs. The expressed goal of the project is to enable as many as possible with reduced work capacity to become part of the workforce (RTV 2002c;RTV 2002b;RTV 2002a).

The daily life of adults with PWS reflects an important political ideal in Norway called *integration*. This means that all inhabitants of the country should equally be offered the same rights and privileges regardless their physical or psychical disability. In the adult population, quality of life is closely related to socially and economically being independent as well as
being a fully accepted and integrated member of society. Being aware of the fact that self-esteem is closely intertwined with joining the work force, using knowledge and skills gained through school and being able to living independently, these adults are enabled to live an as close to normal life thanks to the highly structured and elaborated social security system of Norway.

5.2.1 Sleep Disturbances

This study also showed that four out of the nineteen participants had severe sleep disturbance depicted as sleep apnoea. The fact that approximately 25% of the sample suffered this condition was disclosed, when the subjects before inclusion in the study had their sleep history taken as part of the compulsory and thorough physical health check including an investigation of the sleep pattern.

Severe sleep abnormalities and sleep apnoea is well described in the literature (Clarke et al. 1989; Nixon and Brouillette 2002; Vgontzas et al. 1996) and sleep disturbance and sleep apnoea is also listed as a minor criteria in the Diagnostic Criteria for PWS (Holm et al. 1993). In the part of the population that do not suffer from sleep abnormalities, Excessive Daytime Sleepiness (EDS) is a common feature and is seen in PWS subjects beginning in early childhood (Dykens et al. 1996; Dykens and Kasari 1997). It is found to occur despite increased quality and quantity of nocturnal sleep. Being so prevalent in PWS, EDS has been suggested included in the primary features of the syndrome (Nixon and Brouillette 2002).

Not surprisingly, this qualitatively and quantitatively different sleep pattern influences school performance in a negative way. Children with PWS are easily tired out and tiredness is followed by irritability and difficulties in concentrating. As PWS subjects become adolescent, they seem even more prone to tiredness, maybe as a result of the increasing academic pressure, as well as becoming more obese (Waters 2001). Obesity per se is a well known risk factor for sleep disturbances and sleep apnoea (Butler et al. 2002; Nixon and Brouillette 2002).

According to Norwegian law, all individuals with PWS are entitled an individual educational program, called “IOP” in Norwegian, while being under education (Opplæringslova 2006). When tailoring the individual’s education program, this divergent sleep condition has to be
paid appropriate attention and seriously taken into consideration. Otherwise, sleep problems could increasingly exaggerate the difficulties PWS subjects experience in handling the academic challenges. Together with the decreased cognitive ability in PWS subjects, this could contribute to the described academic underachievement and the maladaptive behaviour seen in the syndrome (Clarke et al. 1989; Whittington et al. 2004a).

5.2.2 Cognitive Function in Relation to Normative Data

The current pilot study clearly showed that the population investigated had a decreased function of working memory, when evaluated by the different tests performed, as part of the CogState battery. In general, comparing populations with normative data is less sensitive to achieving significant differences, as when comparing to a matched population (Maruff and Falleti 2005). The markedly and highly significant differences found in this study underscore the severity of the reduced and divergent learning capacity of our population. The test battery is described to be at least as sensitive to true cognitive changes as conventional neuropsychological tests of memory and attention (Collie, A, et al. 2006), and moreover to have minimal dependence on the cultural, language, and educational background of the tested population (Maruff and Falleti 2005). In an attempt to minimize difficulties in relation to language, we elaborated a specific Norwegian version of the battery for this study. Moreover, each individual was carefully instructed before the test situation.

The findings of the study thus seem to be valid and the differences compared to normal individuals of major importance. In other studies, impairment in memory and attention of 0.5SD has been described as moderate and clinical significant and a change of 0.8 SD has been described as a large change. Impairments of this magnitude are recognised as serious barriers to obtaining meaningful educational and employment experiences (Falleti et al. 2006). In accordance with this, our population must be described as having severe impaired working memory. However, in the ONB test, measuring working memory directly, the speed of performance was within one SD from normative data and significantly a better score than found in the other items, on the other hand the accuracy of the test was markedly decreased. Moreover, no trend was found in correlation between the speed of performance and accuracy of performance. As a consequence, it seems clear that even in the item, where our population scored at best, their function was severely impaired.
These findings should also seriously be taking into account, when preparing individual pedagogic plans for PWS subjects of all ages. We are not able to go into a detailed discussion of the underachievement described in PWS, as we did not explicitly perform any test of intelligence (Clarke et al. 1989; Whittington et al. 2004a). It is however of importance to caution that the CogState test battery has to our knowledge not previously been evaluated in a population with altered and reduced intellectual capacity, as in the present study.

As depicted in Table 5 and in Figure 1, the One Card Learning (OCL) is the test, individuals with PWS on group basis scored best at. Even though all participants performed relatively well on this item, the entire group still scored significantly poorer compared to the normative population. The OCL- tasks measures the speed and the accuracy of the visual memory. According to Baddeley and Logie, the visual as opposed to the spatial property, refers to the visual appearance of an object or scene. The visual memory captures features as the colour, shape, pattern, size as well as the location and orientation of the object relative to one another from a particular point of view in a statistic presentation. (Baddeley and Logie 2004; Logie 1995). As referred to previously, in the theory chapter, in 4.2.5 as well as in the “aspects of internal validity” part of this thesis, the finding confirms that visual memory is the better and even best functioning part of their memory, of the elements measured.

As mentioned in the literature, individuals with PWS perform relatively well on task that require visual-motor coordination and simultaneous problem solving. Our finding concerning detection and thereby psychomotor functioning are incongruent with previous studies (Curfs et al. 1991; Dykens et al. 1992; Gabel et al. 1986). Our findings indicate that the individuals with PWS are relatively slow simultaneous problem solvers or their visual-motor coordination is not, as assumed, so well functioning.

As all tasks require an element of psychomotor functioning, a slow or insecure performance could be at least partly responsible for the diverting and significant findings, as the different items were significantly correlated to DET 1.

The markedly impaired function of working memory in our population could be explained by an inadequate function of central executive (Baddeley and Hitch 1974; Baddeley 1986; Baddeley 2006), or a poor functioning of the episodic buffer which, according to the newest model of Baddeley is responsible for coordination, integrating and storing of
information from the different cognitive systems, rather than the central executive (Baddeley 2000; Baddeley 2002). The central executive is considered of greatest importance for strategy and stimulus processing. It seems therefore responsible for concentrating, learning and being able to carrying out two operations at the same time. By means of the episodic buffer it retrieves information stored in the long-term memory.

Pronounced in their terms, the central executive is responsible for controlling the encoding and retrieval of strategies as well as for focusing, dividing and switching attention and dual-task coordination (Baddeley 2002; Baddeley and Logie 2004; Baddeley 2006). The task that measures the functioning of the central executive in this study is *One Back Learning* (ONB).

The speed of performance of this task was slightly and significantly better than the other tasks. The accuracy of ONB however, showed the most pronounced inter-individual differences in scores within our population (Range from +1 to -15 SD, Table 5).

The *Identification* (IDN) and the *Monitor* (MON) tasks, respectively measure visual and divided attention. The group performances on these two tests are approximately even, however, they might be slightly lower than the above described functioning of ONB (Figure 1), although we could not demonstrate significant differences.

As visual attention is closely related to focusing, concentrating and the ability to sustain attention, performance is related to the functioning of the central executive. Moreover visual attention is also dependent on other factors, like motivation and having a binocular vision. As previously mentioned, we did anticipate that all subjects were motivated for participating, because of them fancying playing card games.

Concerning the binocular vision, the performance of the group could be influenced by the poor vision of some individuals. Eye abnormalities are listed as a minor criterion in Table 1 and are frequently occurring especially in the population with deletion as shown in Table 3. Unmistakeably some subjects squinted while performing the tasks, but that might also be due to a bad habit. A high percentage of the persons tested were wearing glasses, and it is assumed their sight were correct this way.

Divided attention is the ability to attend to more than one stimulus simultaneously. Problems in this area are also related to the functioning of the central executive. In accordance with the
paragraphs above, this component is suggested to be responsible for focusing, dividing and switching attention as well as for concentrating.

In summary, the measured elements of working memory are all closely interrelated. A well functioning working memory is dependent on separately well functioning components, as well as adequate amalgamating and collaboration between the different components. In general the population described had problems with attention, speed and accuracy. All tasks measured are intermingled elements of working memory and on all tasks the individuals scored significantly below the normal and normative comparison population.

5.2.3 Cognitive Function in Relation to Within Group Differences

When analysing within group differences, several points of interest were identified. These findings were found, when the population was divided according to sex, median age and previous treatment with Growth Hormone; an established treatment for children with PWS in Norway as in most Western societies nowadays.

As mentioned, there was a great inter-individual variation in the outcome of the performed tests. This is illustrated in Figure 9 showing individual scores of a well functioning individual, subject 14 compared to a person with a markedly reduced function, subject 1. The figure illustrates the wide range of abilities within the PWS population; from a slightly impaired working memory to a working memory which hardly does work. In a learning setting this wide range means that some individuals will exhibit some problems with learning and making use of what they have learned while others will experience extreme problems.
Figure 9. An illustration of two individuals, where No 1 have score close to normal in several items, whereas No 14 has markedly impaired function most items.

5.2.3.1 Age Dependency
As mentioned, we could not identify any age dependency on our analyses of working memory, as we could have expected. For example, in Down syndrome a progressive decline in IQ has been found throughout adulthood, where an increased risk of early dementia has been described (Pennington and Bennetto 1998).

The age dependency was analysed based on a dichotomisation in relation to the median age of the population. That is, we did not analyse age as a continuous variable but as a categorical variable, simply because of the sample size. A larger population would have allowed a more thorough and in-depth statistical analysis. Still, when looking directly at the individual scores in Table 5, no trends of age dependency were found, even though the age range was from 21 to 38 years. This observation is substantiated by our statistical analysis. Our findings are but, in accordance with CogState measurements in normal adults, where no age dependency of the test battery has been found (Falleti et al. 2006; Maruff and Falleti 2005).
5.2.3.2 Sex Dependency

To our knowledge, differences according to sex in cognitive function in adults with PWS have not previously been described. As given in Figure 4, no significant differences were found in the speed related performances, although there was an overall trend of females scoring better than males. For the accuracy measures however, the females scored noticeably better than males, illustrating a better performance for the items measuring visual memory and working memory. Especially for visual memory capability, the scores for females were remarkable good, within 1 SD of normal, whereas for working memory, even for women the score was far below normal. This indicates the visual attention, the focusing, concentrating and the ability to sustain attention are better in the female part of the population.

The differences between sexes are not explained by other confounders in this study, however could of course be influenced the low sample size, especially of men. As given by Table 4 and Table 5, our men did not perform at the most extreme, however their scores were scattered over the whole range. A potential confounder in relation to sex might be that the test battery favours so-called female skills learned trough upbringing and education due to environmental responses to sex. As a learning effect, the female individuals may have elaborated their skills of precision and correctness. Sex differences though, have not been described in relation to the CogState tests (see Appendix. 1).

5.2.3.3 Cognitive Function in Relation to BMI

As a common phenomenon, the group with the highest BMI had the better scores; only statistical significance was but detected for OCL accuracy, measuring visual memory. The findings indicate that the visual attention, the focusing, concentrating and the ability to sustain attention are better in the population having the highest BMI.

From a statistical point of view confounders of course do exist, yet were not identified. Females were not the most obese as no differences in BMI between the sexes were found. Neither previous treatment with growth hormone which by itself would tend to decrease fat mass was not especially related to BMI. However, we did not perform a multiple regression analysis because of the small sample size and the heterogeneity of our population.

The most fundamental character of individuals with PWS is their demand and search for food followed by obesity and obesity related morbidity (Butler et al. 2002; Holm et al. 1993).
The strategies for treatment have been diet and diet restriction. A potential explanation of our results could be that the best functioning of the individuals are able to manipulate and overcome restrictions, thereby accomplishing satisfaction for their food desire and demand.

On the other hand, it could be speculated that the search and demand for food in PWS is not a primary defect, however secondary to a metabolic defect related to the appetite regulating centre in the hypothalamus. Thus, in order to overcome this defect, the individual has to overfeed. A relative underfeeding caused by restrictions would be followed by impairment in neurological development and thereby impairments in intellectual functioning and memory.

It is well known that nutritional state influences the myelin content (nerve sheets) of the brain. As illustrated by under-nutrition and anorexia nervosa, demyelinisation is followed by mental retardation or early onset of dementia. The process of myelinisation is not restricted to early life but continues in adulthood (Gjærøm 2002). It has to be stated however, that the primary defect at the protein level in PWS has not yet been identified.

5.3.2.4 Cognition in Relation to Previous Treatment with GH

Growth hormone is a metabolic hormone related to growth in childhood and physical performance, body composition, lipid metabolism, and cognition in adults (Faletti, M.G. el al 2006). Although growth hormone secretion seems not to be disturbed in PWS, the metabolism seems to be altered and treatment with GH in children with PWS is now well established (Gjærøm and Grøsvik 2002). Eight of the participants in the present study had previously been treated with GH, a few of them even in adulthood. None had however, been treated within the last year before inclusion in the present study.

The previous treated group scored in general better on the speed related performances than the group that never received GH treatment (Figure 8), though only significantly for the tasks IDN and ONB measuring visual attention and working memory. No differences whatsoever were found for the accuracy related items, neither for the accuracy of working memory.

As discussed in the above paragraphs discussing within group differences, these findings can not be explained by sex or BMI, as these items were not biased by previous GH treatment. The subgroup previous treated with GH was however 5 years younger than the never treated. The difference in performance can not be explained by the age difference between the
groups, as discussed previously and outlined in the publications behind the CogState tests (Collie et al. 2003; Mollica et al. 2004; Silbert et al. 2004), as the performance should not be age dependent in this age group (see Appendix 1).

Our observation has not previously been described in the literature, and as given by the cross sectional design of the pilot study, the finding can only be hypothesis generating. The result will however, be followed in the main protocol of the study, testing the effect of treatment of GH on this population in a randomized controlled setting. It has been shown that GH treatment improves cognition in adults with GH deficiency (Falleti et al. 2006); whether GH treatment improves cognition in adults with PWS, is yet unknown.

5.3 Pedagogic Reflections

When talking of mental retardation we are dealing with a life lasting condition. Although an improved functioning in relation to mental age seldom has been found past primary and secondary school age, it is absolutely possible to stimulate the individual subject within the zone of proximal development (Gjærum and Grøsvik 2002). According to best-known pedagogical principles each individual has to be thoroughly assessed in order to describe strengths and weaknesses in the subject’s cognitive, as well as behavioural profile. In the spirit of Vygotsky’s theory, the optimal assessment should be dynamic (Brown and Ferrara 1985). This is especially important considering the fact underscored by the findings in this study, that the population with PWS is very heterogeneous in their intellectual and behavioural functioning.

On a group basis, the subjects have several features in common (Bertella et al. 2005; Conners et al. 2000; Curfs et al. 1991; Dykens et al. 1992; State MW and Dykens 2000; Stauder et al. 2002; Warren and Hunt 1981). As pointed out, the individuals can be divided genetically into two subtypes with major implications for their functioning (Dykens 2002; Fox et al. 1999; Roof et al. 1999; Roof et al. 2000; Whittington et al. 2004b; Whittington et al. 2004a). However, as found in our pilot study, also within the single genotype (in our study we had almost exclusively individuals with deletion) great inter-individual variation in performance was found. Thus, a throughout workup of the individual should be performed and not primarily be based on medical diagnosis. It is of greatest importance to take the personal
development, previous learning and different aspects of abilities and cognition of each individual into account. This in order to work out and prepare for the most optimal learning conditions.

When planning and performing pedagogic strategies in school, at work or in the living situations the best functioning aspects of cognition should be taken into account. Due to the individual’s genetic difference, their ability to learning has been changed. A different development from time to time needs a different stimulation in order to reach normal development. It might be necessary to think in unconventional terms.

Thus, strategies to improve learning should utilize the individual’s strong visual memory and attention, for example by using visual resources. It is believed that the learning potential of the individuals could be increased by using visual sources, thereby via their best functioning “channel” entering cognition.

It should be emphasised that the individual’s speed of performance is limited by the poor accuracy, as we found in our study. A consequence of this is that the individuals with PWS in a learning setting should be encouraged to reduce speed and thereby expectantly enhancing accuracy. For that reason, and due to the in addition decreased psychomotor function also discovered in our study, it seems not to be a useful approach to stimulate the individual to increase speed of performance.

Not acknowledging these facts could, our adult population, lead to beliefs of not being able to meet expectations of for instance employers and colleagues. Natural consequences of a feeling of shortcoming are sadness, distress or on the other hand, temper tantrums. This very easily leads to negative learning circles.

A special attention and concern should be given males with PWS in all learning settings due to their in general poor performance, if our results can be generalized.

In order to find the right person and job match the huge inter-individual variation in performance also have to be taken into account. A job-match-assessment and an interview could be a viable way in finding the right job. As all individuals in our population had a job which in most aspects was comparable to most people’s weeks of work. Also in work settings, which also should hold developmental aspects, it is of importance that the
individuals are able to cope with the challenges they meet - and feel satisfaction through mastering. Like everybody else, these individuals should realize that their work is valuable and appreciated and to acknowledge that they are respected members of their work team.

To secure that the subject with PWS actually thrives and the job match has been successful periodically evaluation based on as well environmental as well as a personal interviews could be conducted.

That quality of life and personal satisfaction is closely related to perception of mastering and opportunities of personal development should also be recognized when planning independently living for the adult PWS (Zetlin and Morrison 1998). Personal development has to be optimized by balancing the potencies of the individual against requirements of the environment where the subject lives. All adults with PWS living in their own apartment are to a certain degree dependent on the help of a variety of people. Although in consideration of respect for the individual one ought to keep the number of helpers low. Privacy becomes but a joke when people walk in and out of the door. As individuals with PWS have relative strengths at self-help skills (Holm 1981; Thompson et al. 1996) the physical environment should be adapted to the abilities of each subject.

Moreover, leisure time activities and holidays should exhibit genuine understanding and empathy for the subject. Both should be assimilated in accordance with the individual’s interests and capabilities, if personal satisfaction and development is going to be acquired.

In general, the basic ideology of dealing with humans, with or without mental disability should be the same, but in order to treat individuals with PWS they have to be treated inter-individually according to their own strengths and weaknesses. They should be provided full participation and personal autonomy in accordance with personal commitment, motivation and abilities.

It is thus fundamental to go much further than providing basic services. The service provided needs to be individually designed and tailored (Zetlin and Morrison 1998). It is moreover of importance also in adulthood to think in terms of life long learning within the zone of proximal development because all individuals thrive with mastery and cognitive growth.
5.4 Limitations

- Pedagogic and psychological literature on individuals with PWS is sparse. The published studies so far are primarily focusing on genetic and medical aspects, and often based on not well-defined populations (clinical criteria).

- Previous studies on PWS are often heterogeneous, as they have been based on clinical criteria, seldom on genetically verified diagnosis.

- Our pilot study is by design cross sectional. Conclusions have therefore to be taken with cautious and can only be regarded as hypothesis generating.

- Even though the CogState battery worked well in our population, it has previously never been used in a population with mental retardation before. Thereby it is not validated in that context. It could be of major interest to perform studies in other populations, for example in subjects with Down syndrome.

- It is not possible to rule out that our population of adults with PWS is biased from the total Norwegian population with PWS because of the size of the sample, however it seems unlikely. It would additionally have improved the strength of the study, if the sample had a more even sex distribution.

- We did not use a local matched control population, which would have added strength to our study. Our findings were however, highly significant and it seems unlikely that our results would have been qualitatively altered by a more optimal reference population.

- We did not take potential medication in relation to behaviour problems – for example temper tantrums, violent outbursts and obsessive-compulsive behaviour etc. into account.

- The construct validity of the test battery would be improved if it had been validated against “the gold standard”- the Wechsler tests.

- We did focus our test battery on items believed to examine areas of cognition, where the population a priory was expected to perform at best. It would have been valuable,
if the results could be compared with other tests measuring the same areas, as well as other functions of the working memory.

5.5 Conclusions and Further Perspectives

- Theories and classifications of working memory have expanded fast in recent years. Thus, the body of literature has yet not found a unified platform on which research can be performed.

- It has been a dogma that individuals with PWS are difficult to handle in a test situation. The experience of the present study is that adults with PWS are cooperative and positive to deal with, in relation to a time limited, motivating and visual based cognitive test.

- In the pilot study of Norwegian adults with PWS several individuals were found to have severe sleep disturbances demanding treatment. Untreated sleep apnoea might have significant impact on the individual’s daily living and intellectual performance.

- Adults with PWS have markedly decreased working memory as detected with the CogState battery and compared with normative data. The impairment for all items was of major magnitude and exceeds what hitherto have been published in other populations.

- Although markedly reduced, the impairment of visual memory was less pronounced than the other items measured. This should be taken into account, when teaching strategies and learning is considered. Because the visual pathway is clearly the best functioning it primarily ought to be used in instructional, educational and general information settings throughout the lifespan.

- In general, significant correlations between the items measuring psychomotor function and the other items were found. Thus, psychomotor function seems to be central for working memory, at least when tested by CogState.

- Although generally impaired, a huge inter-individual variation was found in performance. Because pedagogic and psychological literature on individuals with
PWS in general is sparse, and educational settings in Norway are unaware of the strengths and weaknesses of this special population, guidelines and teaching manuals should be produced and distributed via Frambu and the school psychologists (the Norwegian PPT) to promote educational settings throughout the country.

- With-in group differences were disclosed in performances. In general female scored better than males and obese better than the less obese. Individuals previously treated with growth hormone performed better than subjects previously not treated. This finding has to be verified in prospective, randomized controlled trials before adults with PWS are offered this medication.
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7. Appendix 1

CogState Normative data

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Date: Thursday, 6 July 2006
Participants
For the detection, Identification, one-back memory and monitoring tasks, data from 879 healthy individuals was used. Of these, 614 were males and 265 were females. Age ranged between 25 and 70 years, and data for each individual was divided into the following age groups: 25-30 years (n = 100); 31-35 years (n = 232); 36-40 years (n = 57); 41-45 years (n = 50); 46-50 years (n = 57); 51-55 years (n = 85); 56-60 years (n = 101); 61-65 years (n = 95); 66-70 years (n = 102).

For the one card learning task, data from 179 individuals was used. Of these, 179 were male and 43 were females. Age ranged between 25 and 70 years, and data for each individual was divided into the following age groups: 25-30 years (n = 30); 31-35 years (n = 23); 36-40 years (n = 12); 41-45 years (n = 12); 46-50 years (n = 8); 51-55 years (n = 13); 56-60 years (n = 28); 61-65 years (n = 26); 66-70 years (n = 2).

Description of tasks

Detection task (DET)
A playing card is presented at the centre of the display. The instruction for the task is written in the “on-screen” helper. That is, “Press YES as soon as the card turns face up. The “K” key is yes” (this is the “D” key if you have entered into the computer that you are left handed).

This task was formerly known as the simple reaction time (SRT) task. It tests psychomotor function.
Identification task (IDN)
A playing card is presented at the centre of the display. The instruction for the task is written in the “on-screen” helper. That is, “Is the face-up card red?” If the answer is yes then press the “K” key, if the answer is no, press the “D” key (reversed for left handed people). Therefore on each trial you must decide whether or not the colour of the card is red.
This task was previously known as the choice reaction time (ChRT) task. It tests simple attentional function.

One-back memory task (ONB)
A playing card is presented at the centre of the display. The instruction for the task is written in the “on-screen” helper. That is, “Is the face-up card exactly the same as the one you have just seen?” If the answer is yes then press the “K” key, if the answer is no, press the “D” key (reversed for left handed people). Therefore on each trial you must decide whether or not the card you are looking at was identical to the immediately previously presented card.
This task tests working memory.

Monitoring task (MON)
Five playing cards are presented next to one another in the middle of the computer screen. Two horizontal white lines are also shown on the screen, above and below the five cards. The instruction for the task is written in the “on-screen” helper. That is, “Press yes as soon as any card touches the white line”. Therefore on each trial
you must monitor each of the cards and press the “YES” key as soon as any one of them touches the line above or below. This task tests **divided attention**.

*One card learning task (OCL)*

A playing card is presented in the centre of the screen. The on-screen helper asks: “Have you seen this card before in this task?”. This task tests **learning**.

**Data Analysis**

Data analysis proceeded in several stages:

1. All response speed data was logarithmic base 10 (log10) transformed prior to analyses to ensure that data met the assumptions of normality and heterogeneity of variance.
2. The sample was then divided into 5 year age bands.
3. For each age band, a group mean score was calculated for each of the outcome measures.
4. Means and standard deviations were derived for each of the age bands.

**Normative tables**

For each cognitive task, a single primary outcome measure was selected from each test in the battery to minimize experiment-wise error rates. Each primary outcome measure was selected because it has been shown to be optimal for the detection of change because:

- a) it is drawn from a data distribution that contains only a small probability of floor or ceiling effects and no restriction in the range of possible performance values [1,2].
b) it is drawn from a distribution that is distributed normally or which can be corrected to normal through the use of appropriate mathematical transformation (e.g., logarithmic base 10, or arcsine) [1,2].

Table 1 summarizes the primary outcome measures for each of the tests in the battery for the GH-pilot study (Note: For one-back memory, both the speed and accuracy of performance can be used).

<table>
<thead>
<tr>
<th>Task name</th>
<th>Unit of measurement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detection</td>
<td>Log$_{10}$ milliseconds</td>
<td>Speed of performance; mean of the log$_{10}$ transformed reaction times for correct responses</td>
</tr>
<tr>
<td>Identification</td>
<td>Log$_{10}$ milliseconds</td>
<td>Speed of performance; mean of the log$_{10}$ transformed reaction times for correct responses</td>
</tr>
</tbody>
</table>
| One back memory    | Log$_{10}$ milliseconds and accuracy | Speed of performance; mean of the log$_{10}$ transformed reaction times for correct responses
AND
Accuracy of performance; arcsine transformation of the proportion of correct responses |
| Monitoring         | Log$_{10}$ milliseconds | Speed of performance; mean of the log$_{10}$ transformed reaction times for correct responses                                           |
| One Card Learning  | Arcsine proportion correct | Accuracy of performance; arcsine transformation of the proportion of correct responses                                                   |
Average means and standard deviations for each task are presented in the following tables.
(Please note: Normative data for the one card learning task is presented separately in the final table.)

### 25-30 years

<table>
<thead>
<tr>
<th>Task</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean + 1SD *</th>
<th>Mean + 2SD *</th>
<th>Mean + 3SD *</th>
</tr>
</thead>
<tbody>
<tr>
<td>DET</td>
<td>Speed</td>
<td>2.425</td>
<td>0.116</td>
<td>2.541</td>
<td>2.657</td>
<td>2.773</td>
</tr>
<tr>
<td>IDN</td>
<td>Speed</td>
<td>2.645</td>
<td>0.111</td>
<td>2.756</td>
<td>2.867</td>
<td>2.978</td>
</tr>
<tr>
<td>MON</td>
<td>Speed</td>
<td>2.481</td>
<td>0.137</td>
<td>2.618</td>
<td>2.755</td>
<td>2.892</td>
</tr>
<tr>
<td>OBK</td>
<td>Speed</td>
<td>2.790</td>
<td>0.104</td>
<td>2.894</td>
<td>2.998</td>
<td>3.102</td>
</tr>
<tr>
<td>OBK</td>
<td>Accuracy</td>
<td>1.22</td>
<td>0.06</td>
<td>1.16</td>
<td>1.1</td>
<td>1.04</td>
</tr>
</tbody>
</table>

* Note: For OBK accuracy, the values were calculated by Mean – 1SD, etc, as lower arcsine values indicate impairment.

### 31-35 years

<table>
<thead>
<tr>
<th>Task</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean + 1SD *</th>
<th>Mean + 2SD *</th>
<th>Mean + 3SD *</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>Speed</td>
<td>2.43</td>
<td>0.08</td>
<td>2.51</td>
<td>2.59</td>
<td>2.67</td>
</tr>
<tr>
<td>CHT</td>
<td>Speed</td>
<td>2.653</td>
<td>0.072</td>
<td>2.725</td>
<td>2.797</td>
<td>2.869</td>
</tr>
<tr>
<td>MON</td>
<td>Speed</td>
<td>2.479</td>
<td>0.098</td>
<td>2.577</td>
<td>2.675</td>
<td>2.773</td>
</tr>
<tr>
<td>OBK</td>
<td>Speed</td>
<td>2.810</td>
<td>0.094</td>
<td>2.904</td>
<td>2.998</td>
<td>3.092</td>
</tr>
<tr>
<td>OBK</td>
<td>Accuracy</td>
<td>1.238</td>
<td>0.054</td>
<td>1.184</td>
<td>1.13</td>
<td>1.076</td>
</tr>
</tbody>
</table>

* Note: For OBK accuracy, the values were calculated by Mean – 1SD, etc, as lower arcsine values indicate impairment.

### 36-40 years

<table>
<thead>
<tr>
<th>Task</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean + 1SD *</th>
<th>Mean + 2SD *</th>
<th>Mean + 3SD *</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>Speed</td>
<td>2.467</td>
<td>0.079</td>
<td>2.546</td>
<td>2.625</td>
<td>2.704</td>
</tr>
<tr>
<td>CHT</td>
<td>Speed</td>
<td>2.688</td>
<td>0.084</td>
<td>2.772</td>
<td>2.856</td>
<td>2.94</td>
</tr>
<tr>
<td>MON</td>
<td>Speed</td>
<td>2.523</td>
<td>0.164</td>
<td>2.687</td>
<td>2.851</td>
<td>3.015</td>
</tr>
<tr>
<td>OBK</td>
<td>Speed</td>
<td>2.839</td>
<td>0.094</td>
<td>2.933</td>
<td>3.027</td>
<td>3.121</td>
</tr>
<tr>
<td>OBK</td>
<td>Accuracy</td>
<td>1.20</td>
<td>0.083</td>
<td>1.117</td>
<td>1.034</td>
<td>0.951</td>
</tr>
</tbody>
</table>

* Note: For OBK accuracy, the values were calculated by Mean – 1SD, etc, as lower arcsine values indicate impairment.
41-45 years

<table>
<thead>
<tr>
<th>Task</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean + 1SD</th>
<th>Mean + 2SD</th>
<th>Mean + 3SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>Speed</td>
<td>2.474</td>
<td>0.130</td>
<td>2.604</td>
<td>2.734</td>
<td>2.864</td>
</tr>
<tr>
<td>CHT</td>
<td>Speed</td>
<td>2.690</td>
<td>0.104</td>
<td>2.794</td>
<td>2.898</td>
<td>3.002</td>
</tr>
<tr>
<td>MON</td>
<td>Speed</td>
<td>2.558</td>
<td>0.162</td>
<td>2.72</td>
<td>2.882</td>
<td>3.044</td>
</tr>
<tr>
<td>OBK</td>
<td>Speed</td>
<td>2.862</td>
<td>0.132</td>
<td>2.994</td>
<td>3.126</td>
<td>3.258</td>
</tr>
<tr>
<td>OBK</td>
<td>Accuracy</td>
<td>1.165</td>
<td>0.097</td>
<td>1.068</td>
<td>0.971</td>
<td>0.874</td>
</tr>
</tbody>
</table>

* Note: For OBK accuracy, the values were calculated by Mean – 1SD, etc, as lower arcsine values indicate impairment.

46-50 years

<table>
<thead>
<tr>
<th>Task</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean + 1SD</th>
<th>Mean + 2SD</th>
<th>Mean + 3SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>Speed</td>
<td>2.532</td>
<td>0.125</td>
<td>2.657</td>
<td>2.782</td>
<td>2.907</td>
</tr>
<tr>
<td>CHT</td>
<td>Speed</td>
<td>2.741</td>
<td>0.110</td>
<td>2.851</td>
<td>2.961</td>
<td>3.071</td>
</tr>
<tr>
<td>MON</td>
<td>Speed</td>
<td>2.543</td>
<td>0.138</td>
<td>2.681</td>
<td>2.819</td>
<td>2.957</td>
</tr>
<tr>
<td>OBK</td>
<td>Speed</td>
<td>2.930</td>
<td>0.167</td>
<td>3.097</td>
<td>3.264</td>
<td>3.431</td>
</tr>
<tr>
<td>OBK</td>
<td>Accuracy</td>
<td>1.128</td>
<td>0.130</td>
<td>0.998</td>
<td>0.868</td>
<td>0.738</td>
</tr>
</tbody>
</table>

* Note: For OBK accuracy, the values were calculated by Mean – 1SD, etc, as lower arcsine values indicate impairment.

51-55 years

<table>
<thead>
<tr>
<th>Task</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean + 1SD</th>
<th>Mean + 2SD</th>
<th>Mean + 3SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>Speed</td>
<td>2.529</td>
<td>0.147</td>
<td>2.676</td>
<td>2.823</td>
<td>2.97</td>
</tr>
<tr>
<td>CHT</td>
<td>Speed</td>
<td>2.739</td>
<td>0.124</td>
<td>2.863</td>
<td>2.987</td>
<td>3.111</td>
</tr>
<tr>
<td>MON</td>
<td>Speed</td>
<td>2.581</td>
<td>0.135</td>
<td>2.716</td>
<td>2.851</td>
<td>2.986</td>
</tr>
<tr>
<td>OBK</td>
<td>Speed</td>
<td>2.924</td>
<td>0.153</td>
<td>3.077</td>
<td>3.23</td>
<td>3.383</td>
</tr>
<tr>
<td>OBK</td>
<td>Accuracy</td>
<td>1.066</td>
<td>0.131</td>
<td>0.935</td>
<td>0.804</td>
<td>0.673</td>
</tr>
</tbody>
</table>

* Note: For OBK accuracy, the values were calculated by Mean – 1SD, etc, as lower arcsine values indicate impairment.
### 56-60 years

<table>
<thead>
<tr>
<th>Task</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean + 1SD *</th>
<th>Mean + 2SD *</th>
<th>Mean + 3SD *</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>Speed</td>
<td>2.545</td>
<td>0.130</td>
<td>2.675</td>
<td>2.805</td>
<td>2.935</td>
</tr>
<tr>
<td>CHT</td>
<td>Speed</td>
<td>2.730</td>
<td>0.089</td>
<td>2.819</td>
<td>2.908</td>
<td>2.997</td>
</tr>
<tr>
<td>MON</td>
<td>Speed</td>
<td>2.593</td>
<td>0.124</td>
<td>2.717</td>
<td>2.841</td>
<td>2.965</td>
</tr>
<tr>
<td>OBK</td>
<td>Speed</td>
<td>2.918</td>
<td>0.105</td>
<td>3.023</td>
<td>3.128</td>
<td>3.233</td>
</tr>
<tr>
<td>OBK</td>
<td>Accuracy</td>
<td>1.168</td>
<td>0.104</td>
<td>1.064</td>
<td>0.96</td>
<td>0.856</td>
</tr>
</tbody>
</table>

* Note: For OBK accuracy, the values were calculated by Mean – 1SD, etc, as lower arcsine values indicate impairment.

### 61-65 years

<table>
<thead>
<tr>
<th>Task</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean + 1SD *</th>
<th>Mean + 2SD *</th>
<th>Mean + 3SD *</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>Speed</td>
<td>2.565</td>
<td>0.126</td>
<td>2.691</td>
<td>2.817</td>
<td>2.943</td>
</tr>
<tr>
<td>CHT</td>
<td>Speed</td>
<td>2.851</td>
<td>0.087</td>
<td>2.938</td>
<td>3.025</td>
<td>3.112</td>
</tr>
<tr>
<td>MON</td>
<td>Speed</td>
<td>2.640</td>
<td>0.166</td>
<td>2.806</td>
<td>2.972</td>
<td>3.138</td>
</tr>
<tr>
<td>OBK</td>
<td>Speed</td>
<td>2.986</td>
<td>0.146</td>
<td>3.132</td>
<td>3.278</td>
<td>3.424</td>
</tr>
<tr>
<td>OBK</td>
<td>Accuracy</td>
<td>1.032</td>
<td>0.135</td>
<td>0.897</td>
<td>0.762</td>
<td>0.627</td>
</tr>
</tbody>
</table>

* Note: For OBK accuracy, the values were calculated by Mean – 1SD, etc, as lower arcsine values indicate impairment.

### 66-70 years

<table>
<thead>
<tr>
<th>Task</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean + 1SD *</th>
<th>Mean + 2SD *</th>
<th>Mean + 3SD *</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRT</td>
<td>Speed</td>
<td>2.607</td>
<td>0.147</td>
<td>2.754</td>
<td>2.901</td>
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</tr>
<tr>
<td>CHT</td>
<td>Speed</td>
<td>2.778</td>
<td>0.114</td>
<td>2.892</td>
<td>3.006</td>
<td>3.12</td>
</tr>
<tr>
<td>MON</td>
<td>Speed</td>
<td>2.638</td>
<td>0.118</td>
<td>2.756</td>
<td>2.874</td>
<td>2.992</td>
</tr>
<tr>
<td>OBK</td>
<td>Speed</td>
<td>3.016</td>
<td>0.150</td>
<td>3.166</td>
<td>3.316</td>
<td>3.466</td>
</tr>
<tr>
<td>OBK</td>
<td>Accuracy</td>
<td>0.939</td>
<td>0.157</td>
<td>0.782</td>
<td>0.625</td>
<td>0.468</td>
</tr>
</tbody>
</table>

* Note: For OBK accuracy, the values were calculated by Mean – 1SD, etc, as lower arcsine values indicate impairment.

**One card learning – All age groups**
<table>
<thead>
<tr>
<th>Age Group</th>
<th>Outcome measure</th>
<th>Mean</th>
<th>SD</th>
<th>Mean - 1SD</th>
<th>Mean - 2SD</th>
<th>Mean - 3SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-30</td>
<td>Accuracy</td>
<td>0.86</td>
<td>0.19</td>
<td>0.67</td>
<td>0.48</td>
<td>0.29</td>
</tr>
<tr>
<td>31-35</td>
<td>Accuracy</td>
<td>0.81</td>
<td>0.17</td>
<td>0.64</td>
<td>0.47</td>
<td>0.3</td>
</tr>
<tr>
<td>36-40</td>
<td>Accuracy</td>
<td>0.74</td>
<td>0.24</td>
<td>0.5</td>
<td>0.26</td>
<td>0.02</td>
</tr>
<tr>
<td>41-45</td>
<td>Accuracy</td>
<td>0.81</td>
<td>0.15</td>
<td>0.66</td>
<td>0.51</td>
<td>0.36</td>
</tr>
<tr>
<td>46-50</td>
<td>Accuracy</td>
<td>0.78</td>
<td>0.24</td>
<td>0.54</td>
<td>0.3</td>
<td>0.06</td>
</tr>
<tr>
<td>51-55</td>
<td>Accuracy</td>
<td>0.83</td>
<td>0.11</td>
<td>0.72</td>
<td>0.61</td>
<td>0.5</td>
</tr>
<tr>
<td>56-60</td>
<td>Accuracy</td>
<td>0.74</td>
<td>0.12</td>
<td>0.62</td>
<td>0.5</td>
<td>0.38</td>
</tr>
<tr>
<td>61-65</td>
<td>Accuracy</td>
<td>0.77</td>
<td>0.16</td>
<td>0.61</td>
<td>0.45</td>
<td>0.29</td>
</tr>
<tr>
<td>66-70</td>
<td>Accuracy</td>
<td>0.83</td>
<td>0.11</td>
<td>0.72</td>
<td>0.61</td>
<td>0.5</td>
</tr>
</tbody>
</table>