1 General Introduction
The meaning of the title of the present thesis is twofold: The Down Side of Pain refers both to the difficulties in pain assessment of people with Down syndrome (DS) and to the pain experience in people with DS. The aim of the thesis is to gain more insight into possibilities for pain assessment and to examine possible alterations in the pain experience of adults with DS. In this chapter, the relevance of examining pain in adults with DS will be first described. Subsequently, knowledge about the pain systems in the brain will be used to make theoretical expectations about the pain experience in DS and the possible relationship with cognitive functioning. Finally, the difficulties of assessing pain in adults with DS will be explained, followed by the outline of the thesis.

**EPIDEMIOLOGY OF DOWN SYNDROME**

Down syndrome (DS) results usually from a third copy of chromosome 21 (i.e., trisomy 21: 95%), while other possibilities are attachment of a part of chromosome 21 to another chromosome (i.e., translocation: 4%) or trisomy 21 in part of the body cells (i.e., mosaicism: 1%) [49]. DS is the most common genetic cause of intellectual disability [6,31,63]. Each year, 245-322 living births are diagnosed with DS in the Netherlands [26,28,80]. The average IQ lies between 30 and 70 [18] and the level of intellectual disability varies from mild to severe [54]. The cognitive profile of DS [16,37,39,42,71] is described in Table 1. Despite an earlier and larger deposition of amyloid beta in the brain [64], clinically evident dementia in DS develops only when the number of neuropathological characteristics of Alzheimer’s disease has increased above a certain threshold [30,32]: this may be 10 to 20 years after the appearance of the first neurofibrillary tangles [32]. In a large sample of Dutch adults with DS aged 45-77 years, 16.8% was diagnosed with clinical dementia [21].

People with DS have a syndrome-specific risk for certain physical conditions, of which some could lead to pain or discomfort, such as middle ear infections and skin problems [10,46]. Especially the musculoskeletal system is vulnerable in DS due to hypermobility of joints, laxity of ligaments, and hypotonia, resulting in a higher prevalence of for example hip and patellar instability, neck pain, scoliosis, and foot deformities [13].
Due to improved medical care, the average life expectancy of people with DS in economically developed countries has increased over the last decennia until almost 60 years of age [27]. An increased life expectancy applies to the total intellectually disabled population, resulting in a larger number of older adults: for example, the proportion aged 50 years and older of the people with intellectual disabilities in the Netherlands is expected to grow from 14% (16,000 people) to 23% (26,000 people) between 2001 and 2020 [86]. The combination of increased life expectancy [27], premature ageing [50], and the aforementioned physical vulnerabilities puts adults with DS at high risk for age-related painful conditions. This is for example reflected in an early onset of cervical or pedal arthritis, sometimes coinciding with gout [2,17,35]. It can be concluded that awareness of the presence of painful and discomforting conditions is especially needed in adults with DS.

<table>
<thead>
<tr>
<th>Relative weaknesses</th>
<th>Relative strengths</th>
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<tbody>
<tr>
<td>Expressive language</td>
<td>Receptive language</td>
</tr>
<tr>
<td>Syntax</td>
<td>Visuospatial working memory</td>
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<td>Verbal working memory</td>
<td>Associative learning</td>
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<td>Set-shifting</td>
<td>Implicit long-term memory</td>
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<td>Dual-task processing</td>
<td>Fluency</td>
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<td>Problem-solving/strategy</td>
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<tr>
<td>Inhibition/perseveration</td>
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<td>Explicit long-term memory</td>
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PAIN PROCESSING IN THE BRAIN AND THE RELATIONSHIP WITH COGNITIVE FUNCTIONING

Pain processing
According to the International Association of the Study of Pain, pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage... Pain is always subjective.” [45]. This definition indicates that pain has various components, and that biological, emotional, and psychological mechanisms are involved. Developments in neuroimaging techniques over the last decades have tremendously increased the knowledge about pain processing by the brain [75], although many complex aspects are not yet understood.

Pain processing in the brain involves ascending and descending pathways (white matter) that connect brain areas (grey matter) [85]. Well-known examples of these pathways are the lateral and medial pain systems, that are named after the thalamic nuclei that are involved [76]. The lateral pain system includes the lateral thalamic nucleus, the insula, parietal operculum, primary sensory cortex, and secondary sensory cortex [68]. This system is involved in pain threshold [33] and is important for the sensory-discriminative aspect of pain: the pain location, intensity, and quality (i.e., stinging or burning) [20,76].

The medial pain system includes brain stem nuclei (i.e., locus coerules and parabrachial nucleus), periaqueductal grey, medial thalamic nucleus, amygdala, hippocampus, insula, hypothalamus, parietal operculum, anterior cingulate cortex, and secondary sensory cortex [68]. This system is involved in pain tolerance [33] and is important for the motivational-affective, cognitive-evaluative, memory-related, and autonomic aspects of pain [69]. The motivational-affective aspect refers to pain unpleasantness, suffering from pain, and the motivation to relief pain [59,70]. The cognitive-evaluative aspect refers to cognitive pain-related functions, such as directing attention to pain, anticipating future implications of pain, appraising the meaning of the pain in relation to the overall context, and rating pain experience on a self-reporting scale [38,59,60,84]. The memory-related pain aspect refers to remembering previous pain experiences [1] and the autonomic pain aspect refers to physical responses to pain, such as changes in heart rate, blood pressure, and skin conductance [56].
A third, less well-studied pathway is the rostral pain system, which is important for behavioural responses to pain [47]. This system shares many brain areas of the medial pain system and is mainly characterized by the involvement of the striatum [47]. The striatum and other parts of the basal ganglia seem to adapt the speed and magnitude of escape/avoid responses on the basis of pain intensity, provide selective attention to facilitate a coordinated motor responses to pain, and send pain information to higher motor brain areas via a gaiting mechanism [19]. Thus, behavioural pain response may be the product of a circuit involving attention, motor preparation, and response selection [74].

The most important brain areas of the lateral, medial, and rostral pain systems are shown in Figure 1.

**Neuropathology and pain assessment**
Knowledge about the neuropathology of brain areas involved in pain processing has provided insight into possible alterations in pain experience in different subtypes of dementia [68], multiple sclerosis [66], Parkinson disease [66], Huntington disease [65], and stroke [83]. For example, lesions of white matter (e.g., the spinothalamic pathway), causing deafferentiation in vascular dementia and stroke, can result in central neuropathic pain: abnormal, intense pain evoked by a non-noxious stimulus such as light touch [55,68,83].

It is argued that the pain experience in DS could be increased or decreased on the basis of neuropathology. A higher pain experience in DS could be caused by small frontal lobes and a low white matter volume in the frontal lobes and brain stem [14,34,57,82]. The pain inhibiting function of these brain areas [22,41] may be disturbed and white matter pathology could increase pain experience [68,83]. In contrast, a lower pain experience in DS might be explained by high concentrations of endogenous opioids leu-enkephalin and dynorphin A [62], and small volumes of hippocampus, amygdala, insula, and anterior cingulate cortex [34,82]. These brain areas process the emotional aspect of pain [40,76].

**Relationship with cognition**
Pain processing and cognitive functioning often share the same brain areas [48,68]. An example of brain areas that have such a double function is the hippocampus, which is involved in episodic and spatial memory as well as in
pain affect \([11,40]\). Similarly, the anterior cingulate cortex is involved in error awareness and conflicting information as well as pain affect \([61,77]\). The frontal cortex is important for planning and working memory, but also for pain inhibition \([12,41,73]\). The insula facilitates attention and working memory to salient stimuli, but also integrates sensory and affective signals for pain processing \([9,44]\).

A functional association between pain experience and cognitive functioning has been demonstrated in both clinical studies and experimental studies. Most of this evidence shows a negative association (i.e., worse cognitive functioning with a higher self-reported pain experience) \([3,23,29,51,53,78,81]\). Possible explanations for a negative association are: 1) cognitive functioning and pain compete for
limited cognitive resources such as attention, 2) pain disturbs neurochemistry of brain areas, and 3) pain disturbs neuroplasticity of brain areas [48]. On the other hand, a positive association (i.e., worse cognitive functioning with a lower self-reported pain experience) has also been found [5, 15, 52, 67]. A possible explanation for a positive association is atrophy of brain areas involved in both neurospychological functioning and pain experience, such as in Alzheimer disease and frontotemporal dementia [68], although a positive association has also been found in elderly without dementia [52].

In sum, the aforementioned functional association implies that a change in cognitive functioning might indicate a change in pain experience. Therefore, knowledge about the relationship between cognitive functioning and pain experience may contribute to pain assessment in people with DS. This is clinically relevant, because adults with DS are at high risk for pain but it is difficult to diagnose their pain, as will be described next.

THE DOWN SIDE OF PAIN

Pain assessment is difficult in people with intellectual disabilities. Caregivers report that recognizing and treating pain in adults with intellectual disabilities is complex [24] (see also Table 2). Difficulties in expressing pain occur, resulting in vague verbal descriptions of pain [25] and ‘challenging behaviour’ that is not recognized as pain behaviour [36]. An adequate pain assessment is essential, because chronic pain could have a negative influence on emotional well-being, quality of life, and adaptive functioning [8, 79], and because under-treatment of pain in people with intellectual disabilities has been reported in the literature [4, 7, 43].

It is important to examine pain experience specifically in adults with DS, for the following reasons: 1) DS is the most common genetic cause of intellectual disabilities [6, 31, 63], 2) people with DS are vulnerable for painful and discomforting physical conditions [10, 46, 58], 3) neuropathology of brain areas involved in pain processing has been studied in DS [14, 34, 57, 62, 82], and 4) it has been clinically observed that people with DS have a tendency to express medical problems as behaviour problems instead of complaining about it, possibly related to their verbal difficulties [72].
**THESIS OUTLINE**

As a first step, two reviews about people with intellectual disabilities were conducted to gain more insight into possible painful physical conditions, pain experience, and behaviour as indicator for pain. **Chapter 2** is a review of musculoskeletal disorders, which could cause pain, in various subtypes of intellectual disabilities (i.e., syndromes) and of possible alterations in pain experience based on neuropathology in these subtypes. **Chapter 3** is a systematic review of categories of behavioural pain indicators in people with intellectual disabilities.

Zooming in on the first meaning of the title of the present thesis, **Chapters 4, 5, and 6** focus on approaches and tools to aid pain assessment in adults with DS. In Chapter 4, different formats are compared to assess comprehension of facial and numeric self-reporting scales for pain. In Chapter 5, comprehension of newly developed pictograms for pain quality and pain affect is examined. Also, both comprehension and preference are compared between facial pictograms and drawn faces for pain affect. In Chapter 6, the use of a newly developed online application for self-reporting pain is evaluated.

Concerning the second meaning of the title of the present thesis, **Chapters 7, 8, 9, and 10** focus on the functioning of the somatosensory system and the pain systems of adults with DS. In Chapter 7, the spinothalamic-mediated sensory functions (i.e., temperature, pain, and crude touch) are assessed with Quantitative Sensory Testing. In Chapter 8, the presence of pain (based on physical conditions and participants’ report) and self-reported pain experience (affect and intensity) are assessed. In chapter 9, the relationship between self-reported pain and cognitive functioning (memory and executive functioning) is examined. In Chapter 10, it is examined whether the presence of apolipoprotein E ε4 allele moderates the relationship between cognitive functioning and self-reported pain experience.
**TABLE 2**
Themes related to pain reported during an interview with 11 caregivers of adults with intellectual disabilities [24]

<table>
<thead>
<tr>
<th>Theme</th>
<th>Summary of answers</th>
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<tr>
<td>Suffering in silence</td>
<td>Recognizing pain is difficult, clients do not complain, perhaps they are afraid for doctors or they do not know the right words, some are 'deliberately hiding pain' (or is this difficulty with expressing emotion?)</td>
</tr>
<tr>
<td>Trying to understand</td>
<td>Be vigilant for verbal signals (complaints) and non-verbal signals (gestures, removing shoes, uncooperative/aggressive, withdrawal, self-mutilation). Pay attention to change in behaviour, mood, body posture, eating, and drinking. Pain expression is individual: know the client to recognize pain.</td>
</tr>
<tr>
<td>Knowledge/abilities</td>
<td>It is useful to share knowledge within the team, to act consistently as a team, and to follow a training for better understanding of pain signals. Discriminate 'exaggerated pain' and 'imagined pain' (both used by clients to receive attention or to avoid participation in activities) from 'real pain' (Findlay: alarming that pain is thought to be exaggerated or imagined).</td>
</tr>
<tr>
<td>Opinion about pain</td>
<td>Clients have higher pain threshold and pain tolerance than the general population (Findlay: misconception). It is unclear whether clients understand what pain is, what the cause is, and how it can be relieved.</td>
</tr>
<tr>
<td>Reducing pain</td>
<td>Rely on professionals to recognize pain. The physician has to ask client or caregiver about the clients’ pain. Can I answer when the physician ask how much pain my client has? Try to reduce pain yourself by using hot-water bottles, massage, and reassuring techniques.</td>
</tr>
<tr>
<td>Emotional impact</td>
<td>Clients with pain do not enjoy activities anymore and are in distress. 'I feel concerned, helplessness, and afraid when I see that he is in pain. I feel frustrated and angry that his pain is not noticed' versus 'It is part of my job, I am used to go to physicians with clients'.</td>
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REFERENCES


