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General Discussion
The objective of the present thesis was to gain more insight into possibilities for pain assessment and to examine possible alterations in the pain experience of adults with Down syndrome (DS). A first strength is that we have concretized the concept of ‘comprehension of the self-reporting scale’ by developing a standard procedure for assessment. The advantages are that this procedure can be used in clinical practice and research and that it aids the reliability of the subsequently reported pain scores. Our ordering format for the Facial Affective Scale is directly related to the subsequent adapted administration of that scale to assess pain experience, in which the number of faces to choose from may be more manageable for people with intellectual disabilities.

A second strength is that a comprehensive approach was used to examine pain in adults with DS (Chapters 8, 9, and 10): both presence and experience of pain, both painful medical conditions and participants’ report, both rest and active movements, both facial and numeric pain scales, and the relationship with cognitive functioning. As far as we know, we were the first to examine the association between cognitive functioning and self-reported pain experience in this clinical population, and also have extended this approach by examining the association with apolipoprotein E (ApoE) genotype. The advantage of the comprehensive approach is that it gained insight into the association between self-reporting the presence of pain and cognitive functioning, and the finding that a worse cognitive functioning in ApoE ε4 carriers with DS does not necessarily imply a different pain experience.

A third strength is that all spinothalamic-mediated sensory functions were included in one study (Chapter 7), that these functions were measured with Quantitative Sensory Testing (QST), and that the relationship with intellectual functioning was addressed. The advantages are that QST reduces variety in somatosensory assessment and that insight into the spinothalamic-mediated sensory functions was further increased by the association with intellectual functioning.

Despite these strengths, not all research questions were answered satisfactorily. The analyses for the association between cognition and self-reported pain experience (Chapters 9 and 10) contained insufficient statistical power, because not all participants reported pain and were able to perform the
neuropsychological tests. Chapters 5 and 6 were pilot studies with small sample sizes. Further, the lacking information about chronicity and severity of medical conditions may have been useful to distinguish pain from discomfort. Finally, the recruitment via care centres for people with intellectual disabilities could have caused an underrepresentation of adults with DS from the community.

A summary of the results that did emerge from the thesis will be described next.

**SUMMARY OF MAIN FINDINGS**

**Review section**

A literature review (Chapter 2) showed that musculoskeletal disorders occur in all of the seven included subtypes of intellectual disabilities (i.e., syndromes): DS, Prader-Willi syndrome, Williams syndrome, Fragile-X syndrome, Rett syndrome, cerebral palsy, and 22q11.2 Deletion Syndrome. Examples of musculoskeletal disorders were scoliosis, arthritis, and instability or dislocation of the joints. It has virtually not been examined how much pain the presence of musculoskeletal disorders causes in these subtypes of intellectual disabilities, while adults in the general population rate some musculoskeletal disorders as being painful. Experimental pain studies show a delayed verbal response to heat and cold-induced pain and a lower heat-pain threshold in people with DS, in contrast to a higher heat-pain threshold pain in Prader-Willi syndrome. On the basis of characteristic neuropathology in pain-related brain areas and pathways, a higher pain experience may be expected in Fragile-X syndrome and 22q11.2 Deletion Syndrome, while pain experience could be both increased and decreased in DS, Williams syndrome, and Prader-Willi syndrome.

In a systematic review (Chapter 3), most of the 27 studies about behavioural pain indicators in people with intellectual disabilities had a methodological quality of 50% on a scale from 0 to 100%. Fourteen categories of behavioural pain indicators were defined, of which motor activity, facial activity, social-emotional indicators, and non-verbal vocal expression were the most frequently reported. Still, it is not always clear that the observed behaviour is caused by pain instead of related factors (e.g., stress or fear) and behavioural pain indicators could differ per individual. Behavioural pain indicators that were found in (young) adults with
DS were facial pallor, restlessness, excessive talking, response to analgesics, and exaggeration of usual symptoms of the disability.

**Clinical section**

After the literature reviews, the next step was to investigate approaches and tools to aid pain assessment in adults with DS. When the comprehension of a numeric scale was assessed thoroughly by not only asking which numbers represent the least pain (0 or 1) and the most pain (9 or 10) but also asking questions about the magnitude of numbers (‘Which is larger: 2 or 8?’ and ‘Which is larger: 6 or 4?’), then fewer adults with DS passed the comprehension test (Chapter 4). Differences in comprehension and preference for facial pictograms as compared to drawn faces were not statistically significant (Chapter 5). Half of the participants understood a series of pictograms for sensory-discriminative quality of pain (burning, stinging, throbbing, and pressing). The current version of an online application for screening of pain experience is too difficult for adults with DS to use without assistance and especially the use of a computer mouse is complex (Chapter 6).

The subsequent step was to investigate spinothalamic-mediated sensory functions (i.e., temperature, pain, and crude touch) and pain experience in adults with DS. Adults with DS were as able as adults from the general population to discriminate with closed eyes warm and cold and to feel monofilaments on the forearms (Chapter 7). Adults with DS with a lower intelligence level were less able than adults from the general population to discriminate sharp from dull. More participants with DS (50%) than adults from the general population (35%) had physical conditions that could cause pain or discomfort (Chapter 8). However, fewer participants with DS (58%) than adults from the general population (73%) reported pain during the test session. Of the participants who reported pain, the average pain experience (i.e., reported by using a facial scale and a numeric scale) was higher in the DS group than in adults from the general population. Adults with DS comprehended the facial scale (75%) better than the numeric scale (43%) and almost 80% comprehended at least one of these scales.

While controlling for age, gender, language comprehension, vocabulary, and the presence of possible painful or discomforting conditions, adults with DS with a worse memory were more likely to report pain (Chapter 9). No statistically significant association was found between cognitive functioning and pain.
experience. The presence of the ApoE ε4 allele in adults with DS did not have a statistically significant association with pain experience or with the relationship between pain experience and cognition, but had a statistically significant association with a worse executive functioning (Chapter 10).

**DISCUSSION**

**The Down Side of Pain**

In the present thesis, the possibilities for pain assessment in DS that were examined included behavioural pain indicators and self-report. Observation of behaviour will especially aid pain assessment in DS when the behavioural pain indicators characteristic of an individual are known. The reduction in the number of adults with DS who passed a comprehension test when a detailed format was used, with a statistically significant reduction for the numeric scale, indicates that such a format is more difficult and consequently more people will fail the test (of whom pain experience will not be assessed). However, the detailed format is preferred for a thorough assessment of the ordinal position of scale items. Irrespective of the format for the comprehension test, adults with DS seem to have a better comprehension of faces than numbers and/or have a better comprehension of pain affect than pain intensity. The use of self-reporting scales for pain is not possible for all adults with DS, as comprehension of facial, numeric, and pictogram scales were related to a higher intelligence level and better language abilities. A shorter, simplified version of the online application STOP-ID! will better meet the aim of a screening tool for frequent, autonomous self-reporting of pain. The STOP-ID! is currently being adapted in cooperation with experts in the field. A second pilot study will be performed in 2015 before the STOP-ID! will be implemented.

The results of the present thesis suggest that the high pain threshold and tolerance that are observed in people with intellectual disabilities [10] might be related to a diminished sharp-dull discrimination ability, although this somatosensory impairment was only found in adults with DS in the lower intelligence range and more research is needed on the psychometric properties of QST in people with intellectual disabilities. The lower number of participants who reported pain during the test assessment in the DS group is in line with clinical observations of a low tendency to complain about pain in adults with DS [26]. Our
results show that the likelihood of reporting the presence of pain is increased in adults with DS with a worse memory. However, the model with memory could only correctly classify 58% in reporting and not reporting the presence of pain and is thus only a partial explanation. The possible lower tendency to report pain, a possible different pain behaviour, and an average pain experience that is relatively low may relate to the experience of caregivers that the recognition of pain in adults with intellectual disabilities is complex and ambiguous [10]. We could not demonstrate a statistically significant association between cognitive functioning and pain experience in adults with DS. It is possible that this was caused by insufficient statistical power, but structural alterations and atypical patterns of brain activation in adults DS [6] arise the question whether the same brain areas for pain experience and cognition are involved and activated in DS as in the general population.

In conclusion, the Down Side of Pain (i.e., difficulties in pain assessment of people with DS) still exists, due to complexities in both pain behaviour and self-report. An example is the negative association between memory and self-reported presence of pain. Despite this, the present thesis has contributed to the search for solutions by describing categories of behavioural pain indicators, developing tools, and showing that comprehension of self-reporting scales is possible in adults with DS. The Down Side of Pain (i.e., the pain experience in people with DS) consists according to the results of the present thesis of a higher self-reported pain experience than adults from the general population and a diminished sharp-dull discrimination ability in adults with DS in the lower intelligence range.

**Recommendations**

**Research**

The results of the present thesis indicate some topics for further research that are clinically relevant for adequate pain management in adults with intellectual disabilities. These topics include: 1) pain experience and pain behaviour characteristic of genetic syndromes with intellectual disabilities, 2) pain experience of pain-related medical conditions, 3) pain treatment, 4) brain activity during pain, and 5) the ability to translate pain experience into scale items. From an ethical view, one must consider whether the burden for people with
intellectual disabilities is proportional to the importance of examining topics that are somewhat less directly related to clinical practice, such as brain activity during pain and the ability to translate pain experience into scale items. Therefore, we will focus on the first three above-mentioned topics.

Chapter 2 showed that the pain experience might be increased or decreased on the basis of syndrome-specific neuropathology. Insight into behavioural pain indicators could help caregivers to recognize pain. As far as the authors know, no clinical studies involving assessment of pain experience in for example Fragile-X syndrome, Prader-Willi syndrome, and Williams syndrome have been performed since our review in 2011. For DS, it its necessary to examine whether pain experience changes with the onset of dementia. People with DS have an increased risk for Alzheimer disease neuropathology [14] and such neuropathology could influence both the pain experience [3,24] and pain treatment [2].

It is often unknown how much pain certain medical conditions cause in people with DS or other aetiologies of intellectual disabilities. This is however clinically relevant information for daily care and pain treatment, because the pain experience may be altered (see Chapter 2) and it is important to know which conditions are causing the most pain to prevent unnecessary suffering. For example, people with DS not only have an increased risk for musculoskeletal disorders [4], but also for cancers such as leukaemia [12,13,23,27], which is a disease involving painful medical procedures [8].

Painful medical procedures relate to the topic of pain treatment in adults with intellectual disabilities, which has been scarcely studied. Concerning DS, a study with a mouse model of DS shows that the morphine dose-response curve was comparable to that of normal mice [20]. Studies based on retrospective data have demonstrated no substantial difference in morphine doses between neonates with and without DS after duodenal and cardiac surgery [7,30], but a larger number of children with DS than without DS received morphine on the third day after cardiac surgery [11]. These retrospective studies provide contrasting results and often contained relatively small sample sizes. It has been stated that research into perioperative and postoperative pain-related behaviour and response to analgesia is needed for people with DS of all ages [31], also because trisomy 21 might alter
pain experience and analgesia requirements due to the location of some pain-related genes on chromosome 21 [16,29].

**Clinical practice**

The main recommendations for clinical practice on the basis of the present thesis concern the following themes: 1) communication about pain, 2) individual pain diagnostics, and 3) multifaceted, multidisciplinary pain assessment.

Communication about the presence of pain should be stimulated by caregivers and medical professionals due to some reasons that people with intellectual disabilities have for not reporting their pain, such as being afraid of doctors, being afraid of the reaction of others, and not wanting to bother others or waste their time [1,9,10]. Research is emerging that addresses the improvement of the communication between general practitioners and people with intellectual disabilities [18,21,32], including practical tools [18] (see also http://sterkeropeigenbenen.nl/). The possibility for self-reporting pain experience should be examined to enhance a sense of self-regulation in people with intellectual disabilities and to obtain clinically relevant information about their pain. Possible tools are self-reporting scales, pictograms, and the online application (adapted version). Communication about sensory-discriminative pain quality (e.g., stinging) may be too difficult, even when the use of pictograms representing pain qualities is practised.

The search for the self-reporting scale for pain that is best comprehended by an individual and the search for the behavioural pain indicators that are characteristic of the individual are vital steps to aid pain diagnostics. Use of the least-most extremes format is minimally required to assess comprehension of a self-reporting scale. However, the individual with intellectual disability should not become frustrated. Family members could provide information about individual-specific pain behaviour. The above-mentioned search for individual pain-related information could be performed by, for example, the multidisciplinary pain team of a care centre for people with intellectual disabilities.

Both self-report and observation of pain behaviour are parts of the recent national guideline ‘Signalling pain in people with intellectual disabilities’ [28]. It is recommended that physiotherapists, physicians, behavioural specialists, caregivers, and family cooperate in the diagnostics, treatment, and management
of pain in people with intellectual disabilities. At this moment, it is too early for a practical contribution of cognitive assessment to pain assessment in DS. Based on the results of the present thesis, no specific recommendation can be made concerning this matter. However, cognitive functioning remains clinically important in the context of pain treatment. Pain generally could have a negative influence on cognition [22] and some cognitive functions are already vulnerable in people with DS [5,15,17,19,25]. The question arises whether the cognitive functioning in DS would further decrease when pain is not adequately treated. Therefore, while the relationship between cognition and pain experience in DS should be examined further with sufficient statistical power, one should remain vigilant to a change in cognitive functioning when people with DS are in pain.

REFERENCES


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