Pain and neuropsychological functioning in adults with Down syndrome

This chapter is under revision as:
ABSTRACT
The aim of the present study was to examine whether neuropsychological functioning (memory and executive functioning) is related to self-reported presence and experience of pain in adults with Down syndrome (DS). Participants were part of a cross-sectional study of 224 adults with DS (mean age 38.1 years; mild-severe intellectual disabilities) in the Netherlands. File-based medical information was evaluated. Self-reported pain presence and experience were assessed (affect with Facial Affective Scale (FAS), intensity with Numeric Rating Scale (NRS)). Neuropsychological tests for memory and executive functioning were used. Participants with lower memory performance were more likely to report the presence of pain, while controlling for age, gender, physical conditions that may cause pain, language comprehension, and vocabulary ($p = .030$, $n = 154$). No statistically significant associations between neuropsychological functioning and pain experience were found. In conclusion, memory seems to be related to the self-reported presence of pain in adults with DS after explicit inquiry. Future research has to show whether this also applies to spontaneous self-report. Because little is known about the relationship between brain anatomy, neuropsychological functioning, and pain experience in DS, the study needs to be replicated with a larger sample size to evaluate whether neuropsychological examination could contribute to pain assessment in DS.

Key words: Down Syndrome, pain assessment, cognitive function, clinical significance.
Many brain areas that process pain are also crucial to neuropsychological functioning [36,49]. For example, the hippocampus is involved in both the affective component of pain and in episodic and spatial memory [4,30], while the prefrontal cortex is important for pain inhibition as well as for working memory and planning [5,31,53]. One could argue that the lessened functioning of brain areas with such a double function coincides with worse neuropsychological functioning and pain processing, resulting in a diminished ability to both report and experience pain. Indeed, research involving elderly people with and without dementia shows that neuropsychological impairment is related to a reduction of pain complaints [32,41,59] and to a lower degree of self-reported pain experience [40,48]. Because a change in neuropsychological functioning might indicate a change in pain experience, neuropsychological assessment is of clinical importance.

The functional association between neuropsychological functioning and pain experience could be useful for pain diagnostics in adults with Down syndrome (DS). DS, the most common genetic cause of intellectual disability [43], is associated with a high risk for painful physical conditions such as hip disorders and neck pain [2,22]. The improved life expectancy of people with DS [17] has increased this risk, as illustrated for example by an early onset of cervical or pedal arthritis, sometimes coinciding with gout [1,6,25]. While pain diagnostics is necessary in adults with DS, it is hampered by a delayed response to pain, a lower tendency to complain about pain, and a higher tendency to express medical problems as problematic behaviour [8,20,52]. To detect pain in time and to better understand the pain experience, a multidisciplinary and multifaceted approach is needed in which neuropsychological functioning could be clinically relevant.

Therefore, the aim of the present study was to examine whether neuropsychological functioning (memory and executive functioning) is associated with the self-reported presence and experience of pain in adults with DS.

MATERIAL AND METHODS

Study design
The design was a cross-sectional study with within-subject comparisons in 224 adults with DS.
Ethical approval
The Medical Ethical Committee of VU University Medical Center Amsterdam (NL33540.029.11) approved the study and informed consent procedure.

Participants
Participants were recruited from 17 care centres for people with intellectual disabilities with locations throughout the Netherlands. Before the start of the study, the care centres’ caregivers and behavioural specialists assessed inclusion and exclusion criteria per client. Other participants were recruited through the Dutch Down Syndrome Foundation website. Inclusion criteria were: being 18 years of age or older, speaking and understanding Dutch, the capability to verbally answer simple questions, and a clinical impression of testability. This latter inclusion criterion implied that adults with DS could participate, regardless of their level of intellectual disability, as long as they could comprehend the instructions for at least some of the tests. Exclusion criteria were: the presence of neurological diseases such as cerebrovascular accidents, tumors, or dementia; the presence of severe visual impairments or hearing loss; and the use of antipsychotics, anticonvulsants or antidepressants, due to possible neuropsychological side effects [18,54]. A previously described method [26] was used to screen for the presence of dementia. This resulted in the exclusion of eight people. The final group consisted of 224 adults with DS. Table 1 shows the group characteristics.

Participants had to provide informed consent to be included in the study. If there was doubt regarding their capacity to provide informed consent, consent was also required from parents or guardians. All tests were performed in a quiet room of the care centre or home where participants lived.

Sample size calculation
According to the statistical program Gpower [13] with $\alpha = .05$, $\beta = .80$, and a medium effect size, the following sample sizes were required: $N = 98$ for relating participants’ report of pain presence with neuropsychological functioning and five covariates (obtained: $N = 147 - 154$), and $N = 85$ for relating self-reported pain experience with neuropsychological functioning and three covariates ($N = 98$ for five covariates in the interaction model) (obtained: $N = 48 - 83$).
### TABLE 1
Demographic and medical characteristics of the participants (N = 224)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number of participants or average value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>$M = 38.1$ ($SD = 11.1$), range 18-65</td>
</tr>
<tr>
<td>Gender: male</td>
<td>118 (53%)</td>
</tr>
<tr>
<td>Living situation: in care centre, or with family</td>
<td>197 (88%), 27 (12%)</td>
</tr>
<tr>
<td>Intellectual disability: mild, moderate, severe</td>
<td>56 (25%), 147 (66%), 21 (9%)</td>
</tr>
<tr>
<td>Estimated intelligence level</td>
<td>201 (87%), $M = 5.0$ ($SD = 1.5$) AE</td>
</tr>
<tr>
<td>Language comprehension</td>
<td>217 (94%), $M = 8.1$ ($SD = 1.6$)</td>
</tr>
<tr>
<td>Vocabulary (years age equivalent)</td>
<td>207 (89%), $Md = 4.1$ ($IQR = 2.0$)</td>
</tr>
<tr>
<td>Sleep problems and/or symptoms of depression</td>
<td>15 (7%); 1 (7%) sleep medication</td>
</tr>
<tr>
<td>Thyroid disorder</td>
<td>76 (34%); 75 (99%) medication</td>
</tr>
<tr>
<td>Diabetes</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>Present analgesics use</td>
<td>10 (5%)</td>
</tr>
<tr>
<td>Physical conditions possible pain/discomfort</td>
<td>113 (50%)</td>
</tr>
</tbody>
</table>

AE = years age equivalent. *a* = The differences between the three subgroups of participants based on intellectual disability levels did not reach statistical significance for age ($H(2) = 0.01, p = 1.0, r = -.001$ to -.01), gender ($\chi^2(2) = 0.56, p = .76, Cramer’s V = .05$), and presence of possible pain/discomfort ($\chi^2(2) = 2.97, p = .23, Cramer’s V = .12$).

**Estimated level of intellectual disability and intelligence**

The level of intellectual disability was estimated by using a previously described method [26]. The level of intelligence was estimated by administering the subtests Block Design and Vocabulary of the Wechsler Preschool and Primary Scale of Intelligence – Revised version (WPPSI-R) [58]. Participants had to construct patterns with blocks within a limited time and to describe the meaning of words. Afterwards, the age equivalents in years and months corresponding to the raw scores of the two subtests were retrieved from the “Manual of Psychodiagnóstics and Limited Ability” [29], and the mean age equivalent was calculated.
Medical information
Caregivers of the participants provided the researcher with file-based medical information. Parents used their personal administration to provide such information. Physical conditions, complaints, and medication administered for painful/discomforting conditions were used to determine the possible presence of pain or discomfort. Using a previously described method [26], one physiotherapist, one general physician, and two specialized physicians for people with intellectual disabilities rated whether physical conditions were likely to cause pain/discomfort.

Language comprehension and vocabulary
Language comprehension was screened by the two sample sentences and the first ten sentences of Sentence Comprehension, a subtest of the Dutch Aphasia Foundation test (Dutch: Zinsbegrip subtest, Stichting Afasie Nederland test; [7]). Participants chose drawings corresponding to sentences that were read aloud by the researcher in a neutral tone. When the researcher noticed that the participant chose randomly, then the instructions were repeated. Possible scores in this study ranged from 0 to 10. For Vocabulary, the age equivalent of the Vocabulary subtest of the WPPSI-R was used.

Neuropsychological assessment
Neuropsychological assessment preceded the pain assessment. The Neuropsychological Test Series for Elderly People with Mild Intellectual Disability (NETOL) [57] was used, which is a Dutch neuropsychological test battery for adults with intellectual disabilities. Most psychometric properties it tests are satisfactory to good [11]. The norms and reliability are not satisfactory, but the present study required merely the use of raw scores and included only subtests with sufficient internal consistency and interrater reliability [56].

The Eight Words Test (NETOL) was used to measure imprinting, direct recall, delayed recall, and recognition of verbal information [55]. A list with eight words was read aloud. Participants were asked to recall as many words as possible, disregarding the order. This was repeated four times (total score 0 – 40). Subsequently, participants were asked to recall the words from the list after a short conversation with the examiner about a random topic (score 0 – 8) and again
after performing the Meander task described below (score 0 – 8). Then, the eight words from the list and eight new words were read aloud and participants had to indicate for each word whether it belonged to the list (score 0 – 16).

The Visual Memory test (NETOL) was used to measure imprinting, direct recognition, and delayed recognition of abstract visual information [55]. Five stimulus drawings were shown; participants had to remember and recognize each one of a set of four drawings. For each stimulus, a maximum of four attempts was provided until the answer was correct: four points were given when the first attempt was successful (total score 0 – 20). Subsequently, the sets of four drawings were shown directly and participants were asked to recognize the five stimulus drawings (score 0 – 5). This last condition was repeated after the Fluency task described below (score 0 – 5).

Executive functioning (EF) refers to meta-cognitive processes that enable efficient planning, execution, verification, and regulation of goal-directed behaviour [38]. The Meander test (NETOL) was considered to measure cognitive flexibility, but also appeals to self-regulation and abstract thinking [55]. Participants had to copy four alternating patterns of geometrical figures (total score 0 – 16). The Fluency test (NETOL) was considered to measure verbal fluency: the ability to name words quickly and efficiently, while inhibiting irrelevant impulses and using strategies [55]. It appeals to semantic memory, but also to EF [9,45]. Participants had to name as many animals as possible within one minute and as many first names as possible within one minute. The Circle Span Backward test (NETOL) was considered a measure for visual-spatial working memory, as it appeals to complex mental tracking and internal visual scanning [55]. The researcher tapped drawn circles in series of increasing length, which participants had to repeat in backward order (total score 0 – 8). The Mazes test (WPPSI-R) was considered to measure the ability to plan and follow a visual pattern [46,51]. Participants had to complete mazes within a limited time per maze while the difficulty increased with each maze (total score 0 – 26).

**Reported presence of pain**
Participants were asked whether they felt any pain at that moment. If this was not the case, then they were asked whether they had felt pain during the day of the test session or in the preceding week. When participants reported pain during any
of these questions, then they were asked to point to the painful location on their own body. If participants felt pain in more locations per test situation, then they were asked to indicate which location was the most painful.

Subsequently, participants were asked to imitate four series of active movements as demonstrated by the researcher: 1) movement of the legs and hips (rising from the chair, walking to the end of the room and back, and sitting again), 2) movement of the neck, shoulders, elbows, wrists, and fingers (moving the chin to the ceiling, to the chest, and to the shoulders, stretching the arms upwards and sideways, stretching the arms forwards and touching the shoulders with the hands, and stretching the arms forwards and “playing the piano”), 3) movement of the back (touching the toes with stretched legs and rotating the torso), and 4) movement of the jaw (opening the mouth as far as possible). By encouraging participants to push the maximum limits of their movement capabilities, pain or discomfort of the involved musculoskeletal structures (i.e., muscles and joints) was provoked during function. Directly after each series, participants were asked whether they felt any pain during the movements and if so, where this was.

**Self-reported pain affect and intensity**

For pain affect, the Facial Affective Scale (FAS) [33,34] was used. This is an ordinal series of nine drawn faces with expressions ranging from no distress to utter distress, with values from 0.04 (maximum positive affect) to 0.97 (maximum negative affect) printed on the back side [34]. Pain affect refers to perceived unpleasantness [42], and is related to pain tolerance and suffering from pain [49]. The examiner asked: “Which face fits best to how the pain makes you feel inside?”

For pain intensity, the numeric side of the Coloured Analogue Scale [33,34] was used. This scale is referred to in the rest of the manuscript as “Numeric Rating Scale (NRS)”. It consists of a vertical “ruler” ranging continuously from 0 to 10 with a plastic slide. A higher score indicated more pain. The examiner instructed: “Please place the plastic slide on the number that shows how much pain you feel.”

Self-reported pain experience was only assessed when participants’ answers on the comprehension test matched the a priori determined answers. The comprehension test had a least-most extremes format for the first 48 participants with DS and an ordering/magnitude format for the rest of the DS group and the
control group. This difference is the result of refining the comprehension test to further increase the reliability.

In the least-most extremes format of the FAS, the nine faces were shown in the original presentation (see Figure 1). Participants were asked which face represents someone with “least pain”. The first and second face (i.e., faces with values .04 and .17 in Figure 1) were considered to be correct for the first question. Participants were then asked which face represents someone with “most pain”. The last face and the one before it (i.e., faces with values .97 and .85 in Figure 1) were considered to be correct. In participants who answered both questions according to the intended answers and who reported pain, pain affect was assessed. The same original presentation of nine faces was shown and participants were asked which face corresponded to the reported pain.

In the ordering format of the FAS, three faces were presented in the order of severe pain, mild pain, and moderate pain (see Figure 2), while participants were asked to arrange the faces in the correct order. In participants who both chose the intended order (from mild to severe pain) and reported pain, pain affect was assessed by using a set of cards (see Figure 3). During each test situation in which pain was assessed, the original option of choosing between nine faces was modified to the option of choosing two times between three faces. Card A was first shown and participants were asked which face corresponded to the reported pain (choice 1). When the left face of Card A was chosen, Card B was shown and participants were again asked which face corresponded to the reported pain (choice 2). When the middle face of Card A was chosen, Card C was shown and participants were asked which face corresponded to the reported pain (choice 2). When the right face of Card A was chosen, Card D was shown and participants were asked which face corresponded to the reported pain (choice 2). The final chosen face from Card B, C, or D was noted.

In the least-most extremes format of the NRS, participants were asked at what level the slide should be positioned when someone has “least pain” and at what level when someone has “most pain” (see Figure 4). Answers that were considered to be correct were 0 or 1 and 9 or 10, respectively. In the ordering format of the NRS, two questions were added that focused on the magnitude of numbers: “Which is larger: 2 or 8?” and “Which is larger: 6 or 4?” In participants
FIG. 1
Faces and their corresponding values of the Facial Affective Scale [33]. This is the backside: the front side (faces without letters and numbers) were presented to participants. Photocopy of test material (first author). Patricia A. McGrath, Pain in Children – Appendix: Pain Assessment, Guilford, New York, United States of America, Copyright © 1990.

FIG. 2
Facial Affective Scale: comprehension test with ordering format. Three faces were presented in the order of severe pain, mild pain, and moderate pain. Participants were requested to arrange the faces from “least pain” to “most pain”. The intended order was from mild to severe pain (corresponding to the McGrath's values of .17, .75, and .85).
FIG. 3
Facial Affective Scale, divided into three different parts. Card A was first shown and participants were asked which face corresponded to the reported pain. When the left face of Card A was chosen, the question was repeated while showing Card B. When the middle face of Card A was chosen, the question was repeated while showing Card C. When the right face of Card A was chosen, the question was repeated while showing Card D.

FIG. 4
who answered all questions according to the intended answers and who reported pain, pain intensity was assessed. The NRS was presented with the plastic slide in the middle and participants were asked to place it on the number corresponding to the reported pain.

For participants who passed the comprehension test according to the intended response but who did not have pain, the FAS value of .04 (corresponding to the face with the lowest pain affect) and the value of 0 (corresponding to the lowest pain intensity) were used, respectively.

**Statistical analysis**

Statistical analyses were performed using SPSS 21. The level of statistical significance was set at $\alpha = .05$ (two-sided). Pain was assessed during the test session in one rest situation and four movement situations. Thirteen participants were not able or willing to perform all four movement situations. For each participant, the number of situations in which pain was reported and the number of painful locations that were reported during the test session were divided by the number of situations completed. The sum of the FAS scores was divided by the number of test situations in which the FAS was used. Similarly, the sum of the NRS values was divided by the number of test situations in which the NRS was used. These measures of average pain affect and average pain intensity were highly correlated ($r_s = .85, p < .001$). Domains of memory (Cronbach’s $\alpha = .83$) and EF (Cronbach’s $\alpha = .76$) were formed by taking the mean of the standardized scores form subtests. These domains were moderately correlated ($r_s = .59, p < .001$).

“Possible pain/discomfort” was based on medical information (e.g., in relation to physical conditions). “Presence of pain” and “self-reported pain experience” referred to the presence and ratings (i.e., affect and intensity) of pain as reported by the participants during the test session.

The main analyses were binary logistic regression analyses and multiple linear regression analyses. All assumptions of the regression analyses were met [14], except for the linearity of the logit assumption for one variable (EF x lnEF). Although this interaction was statistically significant, visual inspection of EF plotted against the logit of the outcome showed no severe violation of linearity, hence the model was run as originally proposed. For theoretical reasons, all regression analyses with neuropsychological functioning were controlled for
age (centered to the mean), gender, and the presence of painful/ discomforting conditions: the binary logistic regression analyses used to explain the reported presence of pain also included language comprehension and vocabulary. Both a simple model and an interaction model (i.e., neuropsychological functioning x age and neuropsychological functioning x painful/ discomforting conditions) were used in the multiple linear regression analyses to explain the pain experience. Multilevel analysis was not necessary. Although it was possible to form a domain of Pain Experience (Cronbach’s $\alpha = .93$) and it was desirable to include both neuropsychological domains in one model, it was decided to perform the multiple linear regression analyses separately for Memory and EF and for pain affect and pain intensity due to the otherwise strong reduction of the sample size and statistical power.

**RESULTS**

**Neuropsychological functioning and reported presence of pain**

The presence of sleep problems and/or symptoms of depression was unrelated to memory ($U = 609.50$, $p = .18$, $r = -.10$), but was related to EF ($t(145) = -2.55$, $p = .012$, $r = -.21$, $M_{\text{with}} = 0.91$, $M_{\text{without}} = 0.14$). However, the presence of sleep problems and/or symptoms of depression was not associated with reporting the presence of pain ($\chi^2(1) = 0.03$, $p = .87$, $\Phi = .01$). Therefore, this variable was not included in the logistic regression analyses.

Table 2 shows that the association between memory and reporting the presence of pain during the test session was statistically significant, while controlling for age, gender, painful/discomforting conditions, language comprehension, and vocabulary. The odds ratio implied that participants with a higher memory performance were less likely to report the presence of pain. In other words, those with a lower memory performance were more likely to report the presence of pain. However, the association between memory and reporting the presence of pain was no longer statistically significant ($B (SE) = -0.64 (0.42)$, $p = .12$) when EF was added to the model. The association between EF and reporting the presence of pain was not statistically significant. The presence of painful/
**TABLE 2**

Binary logistic regressions for variables (potentially) associated with the likelihood of self-reporting the presence of pain

<table>
<thead>
<tr>
<th>Variables</th>
<th>B(SE)</th>
<th>Walds $\chi^2(df)$</th>
<th>$p$</th>
<th>Odds ratio</th>
<th>95% CI for odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
</tr>
<tr>
<td>Memory</td>
<td>-0.76 (0.35)</td>
<td>4.72 (1)</td>
<td>.030*</td>
<td>0.47</td>
<td>0.24</td>
</tr>
<tr>
<td>Age</td>
<td>-0.01 (0.02)</td>
<td>0.43 (1)</td>
<td>.51</td>
<td>0.99</td>
<td>0.96</td>
</tr>
<tr>
<td>Gender</td>
<td>-0.16 (0.35)</td>
<td>0.20 (1)</td>
<td>.65</td>
<td>0.86</td>
<td>0.43</td>
</tr>
<tr>
<td>Possible pain/discomfort</td>
<td>-0.58 (0.34)</td>
<td>2.86 (1)</td>
<td>.091^</td>
<td>0.56</td>
<td>0.29</td>
</tr>
<tr>
<td>Language comprehension</td>
<td>0.13 (0.15)</td>
<td>0.73 (1)</td>
<td>.39</td>
<td>1.14</td>
<td>0.85</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>0.02 (0.03)</td>
<td>0.25 (1)</td>
<td>.62</td>
<td>1.02</td>
<td>0.96</td>
</tr>
<tr>
<td>Executive Functioning</td>
<td>-0.10 (0.32)</td>
<td>0.11 (1)</td>
<td>.75</td>
<td>0.90</td>
<td>0.49</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;0.01 (0.02)</td>
<td>&lt;0.01 (1)</td>
<td>.96</td>
<td>1.00</td>
<td>0.97</td>
</tr>
<tr>
<td>Gender</td>
<td>0.10 (0.34)</td>
<td>0.08 (1)</td>
<td>.78</td>
<td>1.10</td>
<td>0.56</td>
</tr>
<tr>
<td>Possible pain/discomfort</td>
<td>-0.55 (0.35)</td>
<td>2.51 (1)</td>
<td>.11</td>
<td>0.58</td>
<td>0.29</td>
</tr>
<tr>
<td>Language comprehension</td>
<td>0.01 (0.14)</td>
<td>0.01 (1)</td>
<td>.92</td>
<td>1.01</td>
<td>0.77</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>&lt;0.01 (0.03)</td>
<td>&lt;0.01 (1)</td>
<td>.99</td>
<td>1.00</td>
<td>0.94</td>
</tr>
</tbody>
</table>

* = statistically significant. ^ = trend $p < .10$. Age was centered to the mean. Memory model: $\chi^2(6) = 8.56$, $p = .20$, $n = 154$, $R^2 = .05$ (Cox & Snell) and .07 (Nagelkerke), 58.4% correctly classified cases. Executive functions model: $\chi^2(6) = 2.97$, $p = .81$, $n = 147$, $R^2 = .02$ (Cox & Snell) and .03 (Nagelkerke), 59.9% correctly classified cases.
discomforting conditions was associated in a statistical trend with reporting the presence of pain in the memory model, but not in the EF model.

**Neuropsychological functioning and self-reported pain experience**

Of the participants, 173 (79%) comprehended at least one self-reporting scale and 130 (58%) reported pain during the test session. All analyses of the self-reported pain experience included only participants who comprehended a self-reporting scale and reported pain during the test session. The median pain affect was 0.32 ($IQR = 0.25, n = 95$) and the median pain intensity was 2.40 ($IQR = 2.55, n = 60$).

The number of participants who reported pain, were included in the memory or EF domain, and who had sleeping problems and/or symptoms of depression was too small to permit an analysis of the relationship between such problems/symptoms and neuropsychological functioning. The small numbers of these participants limited the likelihood that their presence would influence the results. Associations between thyroid disorder and memory ($U = 960.50, p = .63, r = -.05, n = 97$) or EF ($t (80) = -0.63, p = .53, r = .07, n = 82$) were not statistically significant. Therefore, the presence of sleep problems and/or symptoms of depression and the presence of thyroid disorders were not included as variables in the multiple linear regression analyses.

Table 3 shows the results of the multiple linear regression analyses. Only results concerning neuropsychological functioning will be described. In the simple model, neither memory nor EF had statistically significant associations with self-reported pain experience. No interactions had a statistically significant association with self-reported pain experience.

**DISCUSSION**

**Neuropsychological functioning related to self-reported pain presence**

The first main finding of the present study was a negative association of memory with the likelihood to report the presence of pain by adults with DS. This is in contrast to previous studies in which a worse neuropsychological functioning of elderly people was associated with less pain reporting [32,41,59]. However, it is
### TABLE 3

Multiple linear regressions for variables (potentially) associated with pain experience in participants who reported the presence of pain

<table>
<thead>
<tr>
<th>Model</th>
<th>Variables</th>
<th>Memory and pain affect</th>
<th>Executive functioning and pain affect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$B$ (SE)</td>
<td>$F$ (df)</td>
</tr>
<tr>
<td>1</td>
<td>Cognition</td>
<td>-0.07 (0.04)</td>
<td>3.49 (1, 78)</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>&lt;-0.01 (&lt;0.01)</td>
<td>1.08 (1, 78)</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.07 (0.04)</td>
<td>2.47 (1, 78)</td>
</tr>
<tr>
<td></td>
<td>Possible pain/discomfort</td>
<td>-0.01 (0.04)</td>
<td>0.01 (1, 78)</td>
</tr>
<tr>
<td>2</td>
<td>Cognition</td>
<td>-0.08 (0.04)</td>
<td>1.49 (1, 76)</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>&lt;-0.01 (&lt;0.01)</td>
<td>0.51 (1, 76)</td>
</tr>
<tr>
<td></td>
<td>Gender</td>
<td>-0.06 (0.04)</td>
<td>1.62 (1, 76)</td>
</tr>
<tr>
<td></td>
<td>Possible pain/discomfort</td>
<td>-0.02 (0.04)</td>
<td>0.12 (1, 76)</td>
</tr>
<tr>
<td></td>
<td>Cognition x age</td>
<td>&lt;-0.01 (&lt;0.01)</td>
<td>0.44 (1, 76)</td>
</tr>
<tr>
<td></td>
<td>Cognition x possible pain/discomfort</td>
<td>0.06 (0.08)</td>
<td>0.62 (1, 76)</td>
</tr>
</tbody>
</table>

* = statistically significant $p < .025$ ($p = .05 / 2$ due to the use of two dependent variables). ^ = trend $p < .05$. $\eta^2$ = partial eta squared (effect size). Cognition = neuropsychological functioning. Model 1 = simple model, model 2 = interaction model. Age was centered to the mean. * = change from model 1 to model 2: memory: 0.02 ($p = .53$); executive functioning: 0.02 ($p = .60$).
| Model | Variable                  | Memory and pain intensity |             |       |      |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |       |
|-------|---------------------------|---------------------------|-------------|-------|------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|-------|
|       |                           | B (SE)        | F (df)     | n     | p    | \(\eta^2\) | \(R^2\) model | B (SE) | F (df) | n    | p    | \(\eta^2\) | \(R^2\) model |
| 1     | Cognition                 | -0.34 (0.46)  | 0.54 (1, 52) | 57    | .47  | .01   | .10   | -0.22 (0.49)  | 0.21 (1, 43) | 48    | .65  | .01   | .12   |
|       | Age                       | 0.02 (0.03)   | 0.88 (1, 52) | 57    | .35  | .02   |       | 0.02 (0.03)   | 0.71 (1, 43) | 48    | .41  | .02   |       |
|       | Gender                    | -0.87 (0.49)  | 3.21 (1, 52) | 57    | .079 | .06   |       | -1.13 (0.55)  | 4.24 (1, 43) | 48    | .046^ | .09   |       |
|       | Possible pain/discomfort  | 0.10 (0.49)   | 0.04 (1, 52) | 57    | .84  | <.01  |       | 0.07 (0.56)   | 0.02 (1, 43) | 48    | .90  | <.01  |       |
| 2     | Cognition                 | -0.53 (0.49)  | 0.14 (1, 50) | 57    | .71  | <.01  | .20^  | -1.14 (0.64)  | 0.05 (1, 41) | 48    | .83  | <.01  | .21^  |
|       | Age                       | 0.06 (0.03)   | 3.75 (1, 50) | 57    | .059 | .07   |       | 0.04 (0.03)   | 1.10 (1, 41) | 48    | .30  | .03   |       |
|       | Gender                    | -0.42 (0.51)  | 0.68 (1, 50) | 57    | .42  | .01   |       | -1.41 (0.56)  | 6.28 (1, 41) | 48    | .016*| .13   |       |
|       | Possible pain/discomfort  | -0.40 (0.67)  | 0.35 (1, 50) | 57    | .55  | .01   |       | -0.80 (0.68)  | 1.39 (1, 41) | 48    | .25  | .03   |       |
|       | Cognition x age           | -0.09 (0.05)  | 3.36 (1, 50) | 57    | .073 | .06   |       | -0.01 (0.05)  | 0.05 (1, 41) | 48    | .83  | <.01  |       |
|       | Cognition x possible pain/discomfort | 1.53 (1.29) | 1.40 (1, 50) | 57    | .24  | .03   |       | 2.04 (1.03) | 3.96 (1, 41) | 48    | .053 | .09   |       |

* = significant \(p < .025\) (\(p = .05 / 2\) due to the use of two dependent variables). \(^*\) = trend \(p < .05\). \(\eta^2\) = partial eta squared (effect size). Cognition = neuropsychological functioning. Model 1 = simple model, model 2 = interaction model. Age was centered to the mean. *

\* = change from model 1 to model 2: memory: 0.09 (\(p = .06\)); executive functioning: 0.09 (\(p = .11\)).
unclear whether less pain reporting in elderly people with neuropsychological impairment is caused by a decreased ability to report pain or by a decreased pain experience due to dementia [23]. Our finding is in line with an increased number of pain complaints, both spontaneously and after inquiry, in elderly people with impaired neuropsychological functioning [16]. The authors of that study suggest that neuropsychological impairment may be related to less adequate strategies for coping with pain, as passive coping is related to reporting more pain [19]. We can only speculate whether such a phenomenon also exists in adults with DS. Another possible explanation is that DS adults with an impaired memory are less able during the test session to recall pain from the preceding week and pain during the movement situations, and that this uncertainty may lead to acquiescence (i.e., the tendency to answer “yes” to questions regardless of the content of the questions) [15]. It is important to note that the negative association between memory and reporting the presence of pain was no longer statistically significant when EF was added to the model, which can be explained by the moderate correlation between these two neuropsychological functions ($r_s = .59$). Strictly speaking, the negative association was found for memory including some memory-related EF processes.

**Neuropsychological functioning related to self-reported pain experience**

The second main finding was the absence of associations between neuropsychological functioning and self-reported pain experience that reached statistical significance. A possible explanation is that the required sample size for these analyses was not met due to a large number of participants who did not report the presence of pain (58%). Also, the Bonferroni correction in Table 3 may have been too strict for two dependent variables that are highly correlated (pain affect and pain intensity: $r_s = .85$).

Another explanation is that the functional association between neuropsychological functioning and pain experience is abnormal in DS. Although such a functional association has been demonstrated, for example in chronic pain patients [36,39] and people with dementia [48], structural differences and atypical patterns of brain activation have been found in adults with DS [10]. While much is still unknown about the relationship between brain anatomy and neuropsychological functioning in DS, the brain organization for neuropsychological functions such
as verbal memory and language seems abnormal or even inefficient [35]. Examples of atypical brain activation in DS are reduced frontoparietal connections in rest [21], a thalamus that is less functionally integrated with temporal and occipital regions in rest [21], reduced functional interactions between frontal and temporal regions in rest [3], more activation in cingulate gyrus and parietal lobules than temporal regions during listening to speech [44], no difference in brain activation between listening to forward speech and backward speech [44], and more activation in frontal than occipital and parietal regions during a task involving visual-spatial components [24]. These examples are related to language, (working) memory, directed attention, and visual-spatial ability. As far as we know, no neuroimaging studies of pain in DS have been performed. In short, the question arises whether the same brain areas for neuropsychological functioning and pain experience are involved and activated in DS as in the general population and how neuropsychological functioning and pain experience are functionally associated in DS.

**Strengths and limitations**

The strength of the present study is that, as far as we know, we were the first to study the association between neuropsychological functioning and self-reported pain in DS.

A limitation of the present study is that no distinction between pain and discomfort was made for the physical conditions and that the actual presence of pain experience was uncertain due to the use of self-report. Another limitation is the lack of information about attention, inhibition, and anxiety, while these measures may be significant to the pain experience and the relationship with neuropsychological functioning.

Further, the use of the Social Functioning Scale for Intellectual Disability [28] or the Social Functioning Scale for Intellectual Disability Plus [27] appeared to be incorrect in 12 participants according to the guidelines in the manuals. However, a comparison with a previous measurement of the same questionnaire was still possible to screen for the presence of dementia. Furthermore, for eight participants with DS, the series of movements for the back consisted only of touching the toes: rotation was not yet included in the study protocol of seven participants and was refused by one participant due to back pain. A modified version of the Vocabulary
WPPSI-R subtest was used, because our Dutch translation of 3 of the 12 words differed from forward-backward translation based on guidelines [37] and data collection was too far advanced to make adaptations.

**Recommendations for research**

For a better understanding of the association between memory and the self-reported presence of pain in adults with DS, the present study needs to be replicated as a longitudinal study with repeated measurements. This would be more accurate, because it increases the chance of assessing pain from fluctuating painful conditions such as rheumatoid arthritis [50] and because it decreases the influence of a poor memory on pain recall: the individual only has to reflect on current pain during each of the repeated assessments instead of also recollecting past pain experiences [12,47]. The use of acute painful stimuli (e.g., vaccinations or operations) and intervention studies (e.g., pain treatment) is recommended in combination with repeated measurements of neuropsychological functioning and pain experience to gain more insight into the association between these two components in DS.

**Conclusion**

The results of the current study suggest that adults with DS who have impaired memory functioning are more likely to report pain, but that self-reported pain experience is unrelated to neuropsychological functioning. The findings need to be examined further to better understand the pain experience and to evaluate how neuropsychological assessment can contribute to pain assessment in adults with DS.

**REFERENCES**


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