Utrecht University

Pain in Brain and Body

Research in pain perception, neuropsychiatric problems and cognition in Korsakoff's syndrome

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Name: Thom van der Stadt

Studentnumber: 6386539

1st supervisor(s): Dr. Erik Oudman & Prof. Albert Postma

2nd supervisor: Gini Mathijssen MSc

Abstract

Introduction: Based on health problems in Korsakoff's syndrome, pain can be expected in KS patients. It is still unknown which pain systems in the brain are involved in KS, but in other cognitive impairments higher/lower thresholds for pain have been found. To counter possible awareness problems in KS patients, healthcare reports will be used in this research. The aim of this study is to investigate the pain perception, cognitive functioning and neuropsychiatric problems in KS patients. We hypothesize that patients with KS experience less pain than the acquainted healthcare professionals would score them. *Method*: The sample consisted of 38 patients. The NPI-q and the MoCA-D were used respectively to measure neuropsychiatric problems and cognition in KS patients. The PAIC-15, REPOS, VAS, yes/no questions, and the MPQ-DLV were used to measure pain in KS patients with both patient reports as well as healthcare reports. *Results*: KS patients reported pain significantly lower than their healthcare professionals. However, the patient pain reports did not correlate with the healthcare pain reports. Furthermore, no significant differences have been found between expressions of pain (neuropsychiatric symptoms) and healthcare pain reports. *Conclusion*: KS patients report less pain than healthcare professionals. Furthermore, cognition does not seem to relate to any variable in this research. Although there seems to be no relation between the neuropsychiatric symptoms and both pain reports, a positive relation has been found. All these results suggest that pain is a serious issue in KS patients and that this topic needs more attention for further research.

Introduction

Korsakoff's syndrome (KS) is a neuropsychiatric disorder caused by a thiamine deficiency (Kopelman et al., 2009). KS is most often associated with chronic alcohol consumption (Popa et al., 2021). Due to degradation of the frontocerebellar circuit (consisting of the executive and motor loops) and the Papez Circuit (hippocampus, thalamus, mammillary bodies and cingulate gyrus), individuals with KS typically exhibit cognitive and motor deficits (Segobin et al., 2019; Zahr et al., 2020). The main characteristic cognitive deficits of KS include anterograde and retrograde amnesia, executive and working memory dysfunction, confabulation, apathy, as well as affective and social-cognitive impairments (Arts et al., 2017; Moerman van-den Brink et al., 2019). Van Dam et al. (2019) have reported various behavioral symptoms of emotional or psychological

distress such as restlessness, disinhibition and aggression as neuropsychiatric symptoms. These neuropsychiatric symptoms are associated with higher caregiver burden (Moerman van-den Brink et al. 2020).

Not only do KS patients suffer from cognitive and neuropsychiatric problems, but health problems are also very common in these patients (Kopelman et al., 2009). In the study of Gerridzen and Goossensen (2014) over 50% of Korsakoff patients had at least one comorbid somatic and/or comorbid psychiatric condition. A comorbid condition increases the risk of developing subsequent comorbid conditions and therefore negatively affects health and quality of life (Cohen, 2017). These multiple comorbid conditions will eventually lead to lower quality of life and a reduced life expectancy (Cohen, 2017; van Dam et al., 2019).

Because KS patients often suffer from many comorbid somatic diagnoses, it is reasonable to expect that somatic comorbidities have negative effects on somatic health and therefore might be related to pain (Dong et al., 2020). Pain is regarded as a multidimensional complex experience comprising sensory, affective, and cognitive aspects that can lead to physiological, emotional, and behavioural responses (Defrin et al., 2015). Pain is processed in the brain and body. So, this pain processing is via the main nociceptive pathway and this pathway is the spinothalamic tract (Isa & Chetty, 2021). This tract consists of the medial and the lateral pain system (Scherder et al., 2003). The medial pain system plays a crucial part in the motivational–affective features of pain, involving memory, expectation and emotion, and cognitive–evaluative features, the autonomic–neuroendocrine responses evoked by pain (Hufman & Kunik, 2000: Scherder et al., 2003). Whereas the lateral pain system is particularly involved in the sensory–discriminative features of pain such as recognition of location, intensity and nature of nociceptive stimuli (e.g., sharp or dull) (Scherder et al., 2003). Since the current study focuses on pain perception in Korsakoff's syndrome, this (sub)cortical pain processing in the brain is of relevance (Scherder et al., 2003). It is still unknown which parts of these pain systems are involved in Korsakoff, but it has been confirmed in rodents that the periaqueductal gray, cerebellar and cerebral cortices are involved in increased pain thresholds (Cazuza et al., 2020; Diano et al., 2016). Since these brain areas are also impaired in KS patients, it could be suggested that there might also be higher pain thresholds in KS patients.

Nowadays, it is well established that there are individuals with cognitive impairment with disturbed forms of pain processing of still unknown origin (Lautenbacher et al., 2021). To our

current knowledge, pain perception has not yet been studied in the KS population. Pain has been studied in the Alzheimer and frontotemporal dementia population and these studies are suggesting that this neurocognitive disorder might experience altered pain perception (Cole et al., 2006; Cole et al., 2011; Convery et al., 2020). Some researchers found that people with Alzheimer's dementia may have an increase in the affective component of pain because of higher pain-related activity in sensory, affective and cognitive processing regions (Cole et al., 2006). However, increased or decreased pain was found in patients with frontotemporal degeneration (Convery et al., 2020). In the study of Fletcher et al. (2016), they found that there was a decrease in pain in the behavioral variant of frontotemporal dementia. Overall, studies show opposite patterns of pain perception in different cognitive impairments. Because of these patterns, it could be suggested that different pathways or neural areas are affected in several cognitive disorders. Eventually, this would result in higher or lower pain perception in patients.

From a more recent perspective, there is some tentative evidence that worsening of executive functions is the critical mechanism of the altered perception of individuals with cognitive impairment (Lautenbacher et al., 2021). Several studies have shown that executive functioning is affected in KS. If indeed this executive functioning is critical in pain perception, this could be another reason to expect altered pain experiences in KS. Also, Moerman-van den Brink et al. (2019) have found in their research that executive dysfunction is an important feature of KS, as these deficits may also affect daily functioning. It could be suggested that executive functioning may also play a significant role in pain perception in KS patients (Lautenbacher et al., 2021; Moerman-van den Brink et al., 2019). This means that patients with cognitive impairment are not cognitively flexible and ready to cope with pain (Lautenbacher et al., 2021). So, alteration in a patient's responsiveness to pain may be related to awareness, pain tolerance, cognitive, motivational and behavioral factors, or some interaction of these processes (Fletcher et al., 2016).

It is currently unknown how to accurately assess pain in KS patients. An important aspect of pain perception is illness insight. Since it is generally known that KS patients underestimate their problems regarding quality of life or their psychopathological symptoms, estimating pain perception in patients with KS is difficult (Egger et al., 2002; Steinmetz et al., 2014; Gerridzen et al., 2018). From other populations, such as dementia, it is known that both self-report and proxy-based instruments can be applied to index pain (Amspoker et al., 2021). So, to overcome underestimations of pain, the current research used both self-report and reports from a proxy on

pain perception of the patient, such as a healthcare professional. This approach is based on the research of Oudman et al. (2018) regarding measuring loneliness in KS patients, because KS patients may show difficulties in their bodily awareness.

In this research project, a comparison regarding pain perception in the KS patients was made between the healthcare professionals in the care facility and the patients themselves. Because of illness insight problems in KS patients, difficulties would arise with pain self-reports. So, next to self-reports, other pain measurements were used to observe the patients during this research (Fuchs-Lacelle & Hadjistavropoulos, 2004).

Alongside pain, neuropsychiatric problems of the KS patients were measured in this research project. Atee et al. (2021) studied pain as a contributor to neuropsychiatric symptoms in aged care residents living with cognitive disorders and they found that pain is strongly linked to specific neuropsychiatric behaviors, such as agitation and aggression. Since pain is possibly related to neuropsychiatric symptoms, we decided to measure this in current research.

Taken together, KS patients have serious cognitive and health related issues, suggesting an increased risk for pain. As such the aim of the current study was to investigate the perception of pain, cognitive functioning, and neuropsychiatric problems in KS patients. Based on the present literature about pain in patients with severe cognitive disorders, we hypothesized that patients with KS experience less pain than the acquainted healthcare professionals would score them. Furthermore, we expected neuropsychiatric problems to correlate with the pain within the KS patients. Finally, we wanted to see if there was a correlation between neuropsychiatric problems and cognition within the KS patients.

Methods

Participants

Of the eligible 64 patients diagnosed with Korsakoff's syndrome without comorbid cognitive issues, only 38 patients wanted to participate in this research. The remaining 26 patients refused to participate or were not able to participate. Nonetheless, 38 inpatients (33 male, 5 female; mean age = 65.5; SD = 8.07) and their thirteen primary responsible nurses of the “Korsakoff Center Slingedael” in Rotterdam, The Netherlands participated in this study. In the Netherlands, KS residents living in specialized long-term health care facilities underwent an extended neuropsychological assessment showing extensive memory impairments in accordance with a KS

diagnosis. All selected participants had an extensive history of health issues (broken bones, heart problems, etc.) as this study investigates possible pain perception problems in KS patients. All participants were able to read and speak Dutch. Participants did not receive financial compensation for their participation. Informed consent was obtained via the patient. This informed consent can be found in appendix one. Ethical approval was obtained by an ethical committee of the University of Utrecht.

Materials

The prevalence of neuropsychiatric problems was measured with the Neuropsychiatric Inventory Questionnaire (NPI-Q) (Kaufer et al., 2000). The NPI-Q is a brief questionnaire form of the NPI that was originally developed for the assessment of 12 domains on behavioral and psychological symptoms that are common in dementia. The NPI-Q can be found in appendix two. The Dutch translation used in this study has been demonstrated to be reliable and valid (Gerridzen et al., 2018). The primary nurse completed the NPI-Q for each patient in his/her section. For each symptom, the frequency was assessed with the general screening question: "Has the symptom been present in the last month ('yes' = present, 'no' = absent)?" The severity of the neuropsychiatric problems was measured with the NPI-Q severity subscale. When a symptom had been present in the last month, the caregiver rated the severity of the NPI-Q on a 3-point scale ranging from 1 (mild) to 3 (severe). The NPI-Q total severity score is the sum of the symptom scores and ranges from 0 to 36. Caregiver distress associated with neuropsychiatric problems was measured with the NPI-q distress subscale. This subscale of the NPI-Q provides a reliable and valid measure of subjective caregiver distress in relation to neuropsychiatric problems (Kaufer et al., 1998). The caregiver rated the level of distress experienced in relation to one of the 12 symptoms on a 6-point scale ranging from 0 (no distress) to 5 (severely distressed). The total distress score is calculated by summing the distress scores of the individual symptoms and ranges from 0 to 60.

Cognition in the KS patients was measured with the Dutch version of the Montreal Cognitive Assessment (MoCA-D) (Thissen et al., 2010). This version has also been demonstrated to be reliable and valid (Thissen et al., 2010). The patients themselves completed the MoCA-D and were tested on several domains of cognition. The MoCA-D consisted of the following cognitive domains: memory, visuospatial abilities, executive functioning, language, attention (Nasreddine et al., 2005; Thissen et al., 2010). The total MoCA-D score is calculated by summing

all the points of the several cognition domains and ranges from 0 to 30. The MoCA-D can be found in appendix three.

Subjective pain was measured by a selection of specific pain inventories in this research. Before administering questionnaires, a subjective question about current pain was asked both KS patients and healthcare professionals. The patient was asked if he/she could answer yes/no to the question “do you feel pain at that moment?”, the healthcare professional was asked if he/she could answer yes/no to the question “do you think the KS patient is in pain at the moment?”. Furthermore, a VAS-scale had been used to measure pain in KS patients (Hayes & Patterson, 1921; Verkes et al., 1989). The VAS-scale was used to measure what the KS patients thought about their own pain. Also, this version was translated to Dutch. The Visual Analogue Scale is a non-specific measurement scale, consisting of a horizontal line. The length of this line is 100mm long. On the left side is the minimum score (no pain), on the right side is the maximum score (worst possible pain). The patient should tick perpendicular to the line to what extent he experiences physical pain. The questions that were asked on this scale were: “How severe was your pain on average over the past week (7 days)?” and “How severe was your pain at the worst moments in the past week (7days)?” The number of millimeters between the line indicated by the patient and the minimum score is the score on the VAS. The reliability of the VAS for acute pain measurement appears to be high (Bijur et al., 2001). Due to the lack of awareness in KS patients and regarding the reliability of pain, the VAS-scale was measured twice within approximately two weeks of time. The VAS-scale can be found in appendix four.

To measure the localization of the pain in the KS patients, the MPQ-DLV was used. This is a Dutch version of the Mcgill Pain Questionnaire and is used to measure the complaints of the pain (Verkes et al., 1989). Since there are several pain questionnaires already in this research, only one part of this questionnaire was used. This part was the localization of the pain. This tool consists of a human body from the front and the back. The patient must draw a cross on the body where he/she endures the worst pain. The test-retest correlations of the nine indices and the visual analog pain intensity scales ranged from 0.62 to 0.93 (median: 0.84). Cronbach's alpha coefficients for the indices varied between 0.61 and 0.85 (median: 0.72) (Van der Kloot et al., 1995). The MPQ-DLV can be found in appendix five.

The PAIC-15 is an observational scale to assess pain in persons with impaired cognition (Kunz et al., 2020). This questionnaire is about pain expressions and was filled in by the healthcare

professionals. This tool consists of 15 items divided into three domains with each five items: body movements, vocalizations and facial expressions. Each item has a title and explanation to avoid ambiguity. Each item is scored on a 0 to 3 scale: 0 = not at all, 1 = slight degree, 2 = moderate degree, and 3 = great degree. Also, there is an option "not scorable" for each item. The total PAIC-15 score is calculated by summing all the item scores. The higher the sum, the higher the probability the person is in pain. The 15 items are: Frowning, Narrowing eyes, Raising upper lip, Opening mouth, Looking tense, Freezing, Guarding, Resisting care, Rubbing, Restlessness, Pain-related words, Shouting, Groaning, Mumbling, and Complaining. The PAIC-15 can be found in appendix six. The inter-rater reliability of the PAIC-15 is very high for all three domains (facial expression: 0.91, vocalization items: 0.93, body movements: 0.92; aggregated kappa across domains: 0.92) (Kappesser et al., 2020).

The REPOS (Rotterdam Elderly Pain Observation Scale) was used by the healthcare professionals to assess the behavior of the KS patients that would result in pain (Boerlage, 2008). The REPOS works with an instruction card that describes 10 behaviors that are seen as typical of pain. The observer scores as absent (0) or present (1) after a 2 min observation period. The total scores range from 0 to 10. The REPOS can be found in appendix seven. The REPOS has been determined as a valid and reliable instrument to assess pain in cognitively impaired individuals by several studies (Masman et al., 2018; Boerlage et al., 2021).

Procedure

Patients were obtained via a legal representative that gave consent to recruit these KS patients for this research project, due to reduced mental competencies in these patients. Participants were seen twice within a two-week interval. On both occasions the participant was asked to complete the Visual Analogue Scale (Hayes & Patterson, 1921; Verkes et al., 1989). Within the same month and after completion of the scale, the primary nurse responsible (a healthcare professional) was asked if the patient would feel pain at that moment, with two answer categories: "yes" or "no". The caregiver was unfamiliar with the answers of the patient. After this question, the primary nurse was asked to fill in the NPI-q, REPOS and PAIC-15 for all patients that were enrolled in his/her department of the Korsakoff Centre.

Statistical Analysis

Descriptive statistics were applied to calculate numbers, percentages, means, and standard deviations. Furthermore, Pearson correlation analyses and t-tests (Fisher's exact test and independent t-tests) have been performed. Also, multiple ROC curves have been performed. The Statistical Package for Social Sciences (SPSS), version 22.0, was used for statistical analysis.

Results

All the patients with informed consent were included. One male patient was eventually excluded based on missing values in self-report of pain. So, the total number of participants of this research was 37 patients, and the general characteristics are represented in Table 1.

Table 1

General Characteristics

	M	***SD***
	N = 37	*N = 37*
Age	65.49	*8.07*
MOCA (0-30)	16.86	4.71
REPOS (0-10)	1.68	2.36
VAS (0-10)	2.15	2.57
PAIC-15 (0-45)	8.86	9.68
NPI-Severity (0-36)	4.89	5.19
NPI-Distress (0-60)	5.65	6.83

Pain Perception

Of the 37 patients, 31 reported that they did not feel any pain (84%). However, according to the healthcare professionals 26 patients would not feel pain (70%). To see if this difference was significant and to confirm the hypothesis, a Fisher's exact test was required. In the analysis, patients reported pain as significantly lower than their healthcare professionals ($p < 0.003$). The total distribution of the pain scores of the KS patients and caregivers can be found in Table 2.

Table 2

Cross table pain perception

		Caregiver		
		No	**Yes**	**Total**
Patient	**No**	26	5	31
	Yes	1	5	6
	Total	27	10	37

Etiology

To see if there was any etiology possibly leading to pain, we investigated the medical backgrounds of the patients afterwards. 75.7% of the KS patients had a comorbid somatic diagnosis. 10.8% of the KS patients had a respiratory disease. 5.4% of the KS patients had a digestive disease. Also, there were 3 patients (8.1%) who had diabetes, hypertension or no diagnosis. The etiology of pain can be seen in Table 3.

Table 3

Additional etiology of somatic conditions of the KS patients

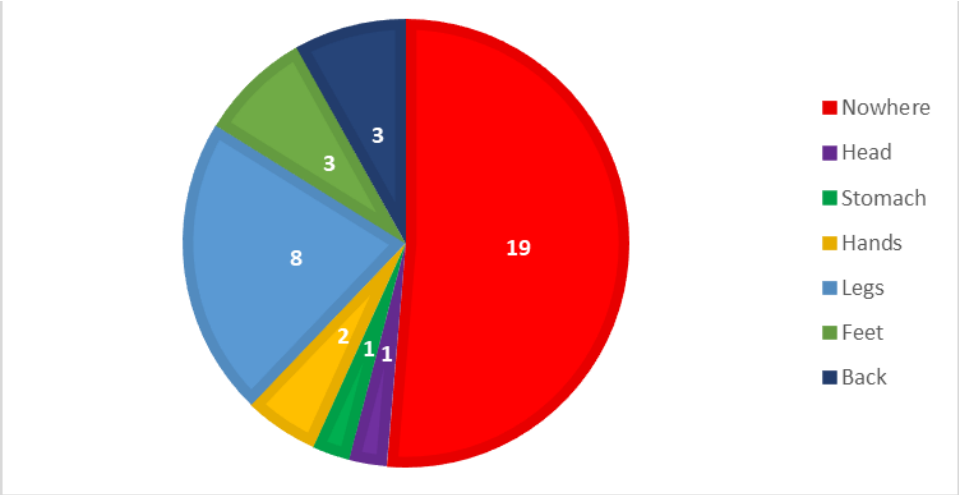
	Frequency	**Percentage**	**Cumulative percentage**
None	1	2.7	2.7
Diabetes	1	2.7	5.4
Respiratory system	4	10.8	16.2
Hypertension	1	2.7	18.9
Digestive system	2	5.4	24.3
Comorbid somatic diagnoses	28	75.7	100
Total	37	100	

Location of Pain

To investigate the pain location on the body, we looked at the distribution of the MPQ-DLV pain localization. Most of the KS patients say they did not feel any pain in their body (51,4%). This means that 48.6% of the KS patients did feel some pain in their body. The total distribution of the pain spots can be seen in Figure 1.

Figure 1

Frequency of the pain location on the body



Expressions of Pain

There was no significant difference between the pain expressions of the patient and the healthcare professional pain score ($t(35) = .18$, $p > .86$). Also, there was no significant difference between the pain movements of the KS patients and the healthcare professional pain score ($t(35) = 1.7$, $p > 0.1$). Moreover, there was no significant difference between the voice sounds of the KS patients and the healthcare professional pain score ($t(35) = 1.2$, $p > .24$).

ROC Curves

The REPOS questionnaire had an area under the curve (AUC) of .36, so this questionnaire cannot discriminate between KS patients with pain or no pain according to Hosmer & Lemeshow (2013). The Visual Analogue Scale had an AUC of .77, so this questionnaire is acceptable to discriminate between patients with pain or no pain (Hosmer & Lemeshow, 2013). The PAIC-15 had an AUC

of .42, so this questionnaire is also not able to discriminate between patients with pain or no pain according to Hosmer & Lemeshow (2013).

Correlations

To look further into the pain of the KS patients and the coherence between other factors such as cognition and neuropsychiatric problems, correlational analysis was performed. Firstly, the reliability of the Visual Analogue Scale interval (e.g., 2 weeks) was performed. A strong correlation was found in the first and second week of the first item of the Visual Analogue Scale (Pearson's r (37) = .716, $p < .001$, two-tailed). In the first week of the first item there was a mean of 2.00, while in the second week a mean of 2.42. Furthermore, a moderate to high correlation was found for the second item of the Visual Analogue Scale in the first and second week (Pearson's r (37) = .633, $p < .001$, two-tailed). For the second item, there was a mean of 2.28 in the first week. In the second week for the second item, there was a mean of 2.82. The difference for those 2 items in these weeks can be explained by a lack of reliability in the KS patient. These results will be explained more in the discussion. For the PAIC-15 a Cronbach's alpha of 0.9 was found, indicating an excellent intern consistency (Gliem & Gliem, 2003) For the NPI-Q a Cronbach's alpha of 0.78 was found, indicating an acceptable intern consistency (Gliem & Gliem, 2003). The VAS-scale did not correlate with the REPOS or the PAIC-15, both healthcare questionnaires, while the REPOS did correlate with the PAIC-15. This result suggested an opposite pattern in healthcare professionals and KS patients regarding pain perception. This result will be elaborated in the discussion. The correlations between the different measurements used in this research are represented in Table 3.

Table 3

Correlations between the measurements - Pearson's analysis

	VAS	MOCA	REPOS	PAIC-15	NPI-Severity	NPI-Distress
VAS	1	.061	-.148	-.125	.067	.062
MOCA	.061	1	-.047	-.075	-.215	-.216
REPOS	-.148	-.047	1	.816**	.524**	.426**
PAIC-15	-.125	-.075	.816**	1	.505**	.427**
NPI-Severity	.067	-.215	.524**	.505**	1	.912**
NPI-Distress	.062	-.216	.426**	.427	.912**	1

** Correlation is significant at the 0.01 level (2-tailed).

Discussion

The current study aimed to explore the perception of pain in KS patients that live in a long-term care facility. It is well known that patients with Korsakoff's syndrome underestimate their problems regarding quality of life or their psychopathological symptoms, reflecting a lack of awareness (Egger et al., 2002; Steinmetz et al., 2014; Gerridzen et al., 2018). Patients often do not have any care demands themselves and are reluctant to receive care, so the patient believes that nothing is wrong with him (Egger et al., 2002). In the present study pain was measured by self-reports and reports of healthcare professionals in the long-term care facility. We have no reason to assume that the sample of the current research is not representative, because of the clinical characteristics of the participants and non-participants. Results showed that most of the KS patients do not report any pain, while their medical backgrounds suggested comorbid medical conditions that would have been likely to result in pain. Healthcare professionals scored the pain of the KS patients higher than the patients themselves, but the magnitude of discrepancy was not that large. Also, the pain reports of the healthcare professionals and KS patients are positively related to the severity of the neuropsychiatric symptoms. Although there seems to be no association between the pain reports of the KS patients and the severity of the neuropsychiatric symptoms. Furthermore,

cognition does not seem to relate to any variable in this research. All these results suggest that pain is a serious issue in KS patients and that this topic needs more attention for further research. Especially because the KS patients can't tell they are in pain when they clearly are according to healthcare professionals.

The pain level of pain in this present study was overall not high, both in the self-reports for the patients as well as the healthcare professionals that rated the pain level of the patients. Approximately, half of the European nursing home residents suffer from pain (Steenbeek et al., 2021). While in this research over 70% of the KS patients do not report pain. This suggests that pain perception that pain is certainly underestimated in Korsakoff's syndrome and that it needs attention in these clinical facilities. This is important to note because pain is related to somatic comorbidity and the negative outcomes such as the risk of developing subsequent comorbid conditions and lower health and quality of life (Cohen, 2017; van Dam et al., 2019). Earlier studies have shown pain in patients with cognitive impairments (Cole et al., 2006; Cole et al., 2011; Convery et al., 2020; Fletcher et al., 2016). We are the first to explore pain in Korsakoff's syndrome. The results of this study suggest that KS patients differ from other patients in pain perception, so the research of pain perception in KS patients has become even more important.

In this study, the healthcare professionals reported higher pain levels than self-reports of pain in patients with KS. This result is not in line with other research done with elderly patients in nursing homes (Horgas & Dunn, 2001). Horgas and Dunn (2001) found that the patients reported more pain than the healthcare professionals and this may suggest that pain perception is specifically different in KS patients from other elderly patients. In former research the caregivers reported lower pain levels than the patients in the nursing homes. However, the most striking finding in this study was that there was no association between the healthcare professionals scores and the self-reports of the patients (Horgas & Dunn, 2001). This pattern is also seen in the current study, where there is also no congruence between healthcare professionals and patients. As stated before, estimating pain in KS patients is difficult, since it is generally known that KS patients underestimate their problems regarding quality of life, reflecting a lack of awareness (Egger et al., 2002; Steinmetz et al., 2014; Gerridzen et al., 2018).

Subsequently, the pain questionnaire for the KS patients (VAS) and the pain assessments for the healthcare professionals didn't seem to be related (PAIC-15 and the REPOS). This also means that there is no congruence between the healthcare reports and the patient reports. An

explanation for this result could be that many individuals avoid discussing pain unless they are asked about it directly (Curtiss, 2010). Patients may not want to complain, may assume pain is an inevitable consequence of cancer or aging, or may not realize that pain can be ameliorated. Other possible explanations could be that healthcare professionals have a lack of knowledge about pain management (Yates et al., 2002; Zwakhalen et al., 2018) and that the pain assessment scales may not be sufficient specifically for KS patients, based on the results from this current research.

Another reason for differences between self and other reports could follow from the observed correlation between pain and neuropsychiatry. It might be that healthcare professionals weigh more neuropsychiatry also in their judgments about pain rather than pain itself (Gagliese et al., 2018). Regarding this explanation, it could clarify the correlation between the neuropsychiatric scores in the healthcare reports and the pain in KS patients. The relation between neuropsychiatry and pain is in line with research about other cognitive impairments such as dementia. Atee et al. (2021) found in their research that pain is a contributor to behavioral changes in aged care residents. As these neuropsychiatric symptoms such as restlessness, disinhibition, and aggression have been associated with higher caregiver burden, interventions are highly needed for these behavioral problems (Moerman van-den Brink et al. 2020). Another possible explanation for the correlation between neuropsychiatric symptoms and pain could be that the questionnaires measuring these variables overlapped too much. A strong correlation between neuropsychiatric symptoms and pain could suggest that pain is an underlying factor of neuropsychiatric symptoms in KS. It also could be that the pain questionnaires don't measure pain but the neuropsychiatric severity and distress. For further research it could be interesting to see how pain and neuropsychiatric symptoms relate to each other and if new measurements are needed for these variables.

On the other hand, no correlation was found between cognition and neuropsychiatric problems in KS patients. This result is not in line with the study of Trivedi et al. (2013) and Lü et al. (2021). These researchers found that neuropsychiatric symptoms increase both in frequency and severity with increasing cognitive decline, while in this research there seems to be no relation between these factors. A possible explanation for this could be that the studies that found a correlation made a regression analysis between the different domains of cognition and the different neuropsychiatric symptoms. While in this research, we only compared cognition and neuropsychiatric symptoms as total variables. For further research the neuropsychiatric symptoms

should be divided into different symptoms and should be compared solely to the different cognition domains in KS patients.

Taken together, these findings illustrate the unnoticed pain of KS patients and the complexities of assessing pain in KS patients since the overall pain scores were low in our study despite the somatic comorbidities. It is relevant to devote new research into this pain perception problem within KS patients. A suggestion for further research could be to look further into the pain pathways in the body of the KS patients, meaning the medial and lateral pathways (Scherder et al., 2003). Also, the need to include caregivers in educational programs focusing on managing pain in elderly nursing home residents is growing rapidly (Horgas & Dunn, 2001; Dequeker et al., 2018). Therefore, pain should never be seen outside the context of psychiatric problems with Korsakov.

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Appendix 1

Informatie Brief en Informed Consent

Informatie voor deelnemers van deze onderzoek:

Titel Studie: ‘Pain perception, neuropsychiatric problems & cognition in Korsakoff's syndrome’

Uitvoerenden onderzoek:
Thom van der Stadt – t.p.vanderstadt@students.uu.nl 0617908965
Begeleider: Prof. Dr. Albert Postma - A.Postma@uu.nl
Externe Begeleider: Dr. Erik Oudman- e.oudman@leliezorggroep.nl

Datum, plaats: XX.XX.2021, Rotterdam, Nederland

Beste dames en heren, Met deze brief, willen we u graag uitnodigen om deel te nemen aan het onderzoeksproject ‘Pain perception, neuropsychiatric problems and cognition in Korsakoff's syndrome’.

Wat kan u verwachten als een deelnemer?

Dit onderzoek bestaat uit twee delen. Het eerste deel vindt plaats in het Korsakovcentrum Slingedael in Rotterdam. Uw taak zal zijn om deel te nemen aan verschillende vragenlijsten en een aantal vragen van de onderzoeker. Na ongeveer 2 weken zal de onderzoeker nogmaals langskomen bij het Korsakovcentrum Slingedael in Rotterdam om een aantal vragenlijsten af te nemen en daarbij een aantal vragen te stellen aan u.

Vertrouwelijkheid of verwerking van data

In dit onderzoek is het noodzakelijk om persoonlijke data op te slaan. We hebben deze data nodig om onze onderzoeksvraag fatsoenlijk te beantwoorden of om u te contacteren voor eventuele toekomstige onderzoeken. De persoonlijke data zal worden opgeslagen op een andere computer dan de data van het onderzoek. De computer waar deze persoonlijke data is opgeslagen is beveiligd volgens een strikt protocol. Alleen onderzoekers betrokken bij dit onderzoek hebben toegang tot uw persoonlijke data. De data van het onderzoek zal worden beveiligd met een wachtwoord. Alle data, betreffende de persoonlijke en van het onderzoek, zal 10 jaar worden bewaard. Dit is in overeenstemming met de richtlijnen van de VSNU Association of Universities in the Netherlands.
Voor meer informatie over uw privacy, verwijzen we u naar https://autoriteitpersoonsgegevens.nl/nl/onderwerpen/avg-europese-privacywetgeving.

Vrijwillige deelname

Deelname aan dit onderzoek is volledig vrijwillig. Op ieder moment in het onderzoek kunt u beslissen om niet langer deel te nemen. Als de deelname wordt beëindigd zullen we de data bewaren tot het moment van beëindigen mits u hier geen toestemming voor geeft. Als u toestemt om deel te nemen aan

dit onderzoek vragen we u vriendelijk om het bijgevoegde formulier te ondertekenen en in te leveren bij één van de onderzoekers.

Met vriendelijk groet,
Thom van der Stadt
Prof. Dr. Albert Postma
Dr. Erik Oudman

Hierbij verklaar ik:

Ik heb de informatiebrief over het onderzoek [‘Pain perception, neuropsychiatric problems & cognition in Korsakoff's syndrome’] gelezen. Ik kon aanvullende vragen stellen. Mijn vragen zijn afdoende beantwoord. Ik had genoeg tijd om te beslissen over deelname.

Ik weet dat indien ik vragen of bedenkingen heb rond mijn deelname aan het onderzoek dat ik dan contact kan opnemen met een van bovengenoemde onderzoekers. Ik kan verzoeken om informatie te ontvangen over de resultaten van het onderzoek op groepsniveau.

Ik weet dat meedoen helemaal vrijwillig is. Ik weet dat ik op ieder moment kan beslissen niet langer mee te doen. Daarvoor hoef ik geen reden te geven.

Ik weet dat mijn onderzoeksgegevens na het onderzoek nog 10 jaar na publicatie bewaard worden en daarna worden vernietigd. Ik weet dat sommige mensen mijn gegevens kunnen inzien. Personen die mijn gegevens in kunnen zien zijn bijvoorbeeld monitors, auditors, en leden van het onderzoeksteam.

Ik weet dat mijn gegevens altijd uiterst vertrouwelijk behandeld zullen worden.

Ik geef toestemming om mijn gegevens te gebruiken voor onderzoekpublicaties, op voorwaarde dat de gegevens in de publicaties volledig geanonimiseerd zijn en niet op mijn persoon terug te leiden zijn.

Naam Handtekening deelnemer

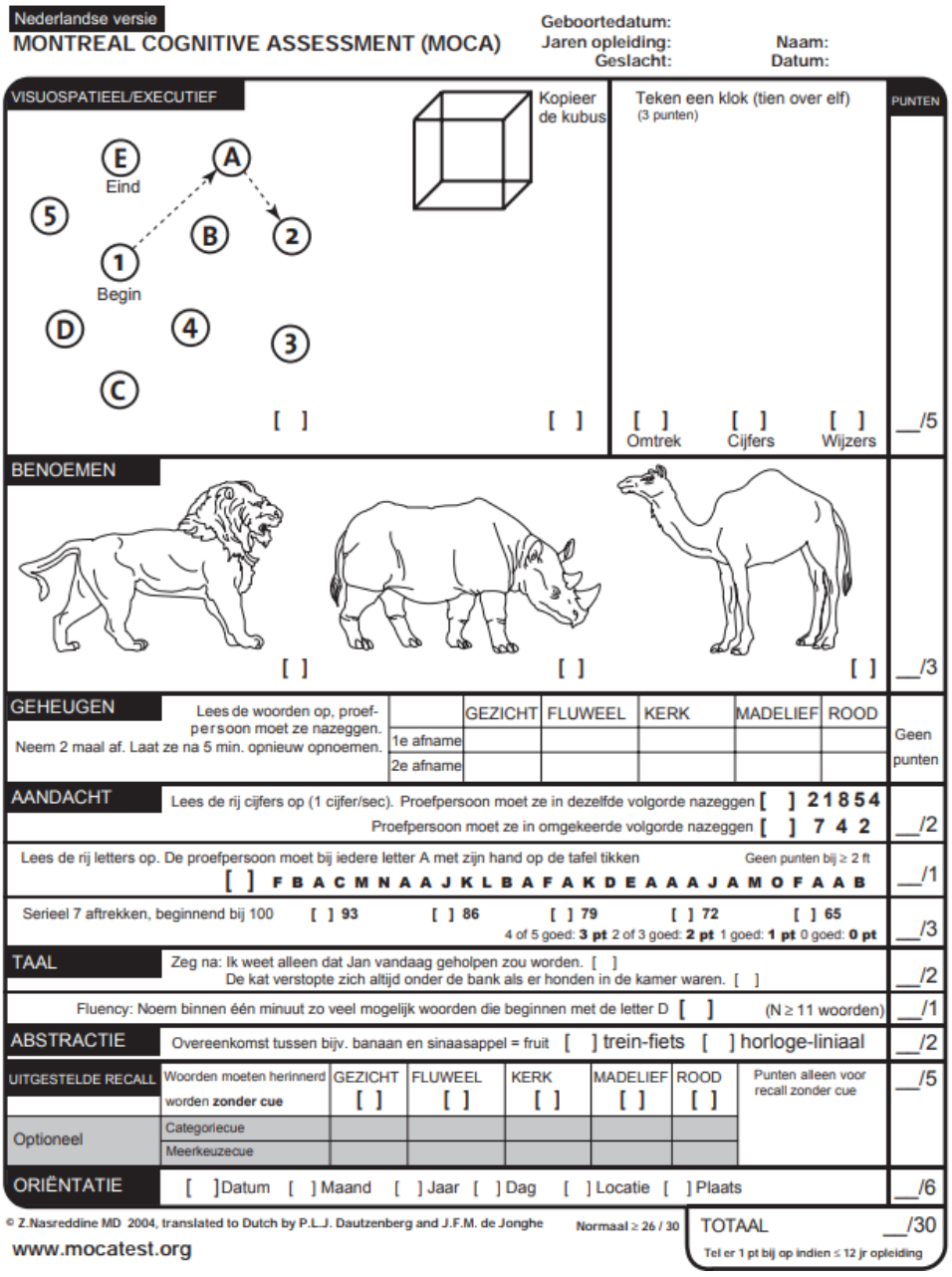
Datum Handtekening onderzoeker

Appendix 2: De Neuropsychiatrische Vragenlijst-Questionnaire (NPI-Q) D. Kaufer, MD and J.L. Cummings, MD Nederlandse vertaling J.F.M. de Jonghe, M.G. Kat en C.J. Kalisvaart

Wilt u bij het beantwoorden van deze vragen steeds uitgaan van veranderingen die zich hebben voorgedaan vanaf het moment dat hij geheugenproblemen kreeg. Omcirkel alleen “Ja” indien het symptoom in de afgelopen maand aanwezig was. In andere gevallen omcirkelt u “Nee”. Voor elke vraag die u met “Ja” beantwoordt: a) Beoordeel de ERNST van het symptoom (hoe beïnvloedt het hem): 1 = Licht (merkbaar, maar geen belangrijke verandering) 2 = Matig (belangrijk, maar geen ingrijpende verandering) 3 = Ernstig (erg duidelijk of opvallend, een ingrijpende verandering) b) Beoordeel de mate waarin het symptoom voor u EMOTIONEEL BELASTEND is (hoe het u beïnvloedt): 0 = In het geheel niet belastend 1 = Minimaal (enigszins belastend, geen probleem om mee om te gaan) 2 = Licht (niet erg belastend, meestal makkelijk om mee om te gaan) 3 = Matig (nogal belastend, niet altijd makkelijk om mee om te gaan) 4 = Ernstig (erg belastend, moeilijk om mee om te gaan) 5 = Zeer ernstig/extreem (uiterst belastend, niet in staat er mee om te gaan) Beantwoordt de vragen zorgvuldig. Vraag gerust om uitleg indien nodig.

	ja nee	Ernst	Emotionele belasting
Wanen Is hij/zij overtuigd van bepaalde gedachten, waarvan u weet dat ze niet waar zijn; denkt hij/zij bijvoorbeeld dat andere mensen hem/haar kwaad willen doen of van hem/haar stelen?	ja nee	1 2 3	0 1 2 3 4 5
Hallucinaties Hallucineert hij/zij; ziet hij/zij iets, dat er niet is, of hoort hij/zij geluiden of stemmen die een ander niet kan horen?	ja nee	1 2 3	0 1 2 3 4 5
Agitatie/Agressie Komt het voor dat hij/zij weigert mee te werken of zich niet laat helpen door een ander? Is hij/zij lastig om mee om te gaan?	ja nee	1 2 3	0 1 2 3 4 5
Depressie/Dysforie Lijkt het alsof hij/zij verdrietig of depressief is, of zegt hij/zij dat hij/zij zich somber voelt?	ja nee	1 2 3	0 1 2 3 4 5
Angst Raakt hij/zij overstuur of wordt hij/zij zenuwachtig wanneer u (of verzorgende) weggaat? Is er nog iets anders dat erop wijst dat hij/zij angstig is; zoals naar adem happen, zuchten, zich niet kunnen ontspannen of erg gespannen voelen?	ja nee	1 2 3	0 1 2 3 4 5
Euforie/Opgetogenheid Lijkt hij/zij zich te goed of te opgewekt te voelen?	ja nee	1 2 3	0 1 2 3 4 5
Apathie/Onverschilligheid Lijkt hij/zij minder geïnteresseerd te zijn in zijn/haar gewone activiteiten of in de activiteiten en plannen van een ander?	ja nee	1 2 3	0 1 2 3 4 5
Ontremd gedrag Handelt hij/zij impulsief zonder over de gevolgen na te denken? Praat hij/zij bijvoorbeeld tegen onbekenden alsof hij/zij ze goed kent, of maakt hij/zij kwetsende of tactloze opmerkingen tegen anderen?	ja nee	1 2 3	0 1 2 3 4 5
Prikkelbaarheid/Labiliteit Is hij/zij ongeduldig of snel geïrriteerd? Kan hij/zij er niet goed tegen als iets vertraagd is of als hij/zij moet wachten op een geplande activiteit?	ja nee	1 2 3	0 1 2 3 4 5
Doelloos repetitief gedrag Doet hij/zij telkens dezelfde handelingen, zoals doelloos rondlopen in huis, peuteren aan knopen, ergens aan plukken, draadjes opwinden en dergelijke?	ja nee	1 2 3	0 1 2 3 4 5
Gedrag 's nachts Maakt hij/zij u 's nachts wakker; staat hij/zij te vroeg op of doet hij/zij te vaak een dutje overdag?	ja nee	1 2 3	0 1 2 3 4 5
Eetlust/eetgedrag Is hij/zij afgevallen of in gewicht aangekomen, of is zijn/haar voorkeur voor bepaald eten veranderd?	ja nee	1 2 3	0 1 2 3 4 5
Totaal			

Appendix 3: Montreal Cognitive Assessment (MOCA) Nasreddine Z (1996); Nederlandse versie: Dautzenberg PLJ, de Jonghe JFM (2004)



Nederlandse versie

MONTREAL COGNITIVE ASSESSMENT (MOCA)

Geboortedatum:
Jaren opleiding: Naam:
Geslacht: Datum:

VISUOSPATIEEL/EXECUTIEF — PUNTEN

Kopieer de kubus

[ ] [ ]

Teken een klok (tien over elf) (3 punten)

[ ] Omtrek [ ] Cijfers [ ] Wijzers __/5

BENOEMEN

[ ] [ ] [ ] __/3

GEHEUGEN — Geen punten

Lees de woorden op, proefpersoon moet ze nazeggen. Neem 2 maal af. Laat ze na 5 min. opnieuw opnoemen.

	GEZICHT	FLUWEEL	KERK	MADELIEF	ROOD
1e afname					
2e afname					

AANDACHT __/2

Lees de rij cijfers op (1 cijfer/sec). Proefpersoon moet ze in dezelfde volgorde nazeggen [ ] 2 1 8 5 4

Proefpersoon moet ze in omgekeerde volgorde nazeggen [ ] 7 4 2

Lees de rij letters op. De proefpersoon moet bij iedere letter A met zijn hand op de tafel tikken — Geen punten bij ≥ 2 ft __/1

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

Serieel 7 aftrekken, beginnend bij 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65 __/3

4 of 5 goed: **3 pt** 2 of 3 goed: **2 pt** 1 goed: **1 pt** 0 goed: **0 pt**

TAAL __/2

Zeg na: Ik weet alleen dat Jan vandaag geholpen zou worden. [ ]

De kat verstopte zich altijd onder de bank als er honden in de kamer waren. [ ]

Fluency: Noem binnen één minuut zo veel mogelijk woorden die beginnen met de letter D [ ] (N ≥ 11 woorden) __/1

ABSTRACTIE Overeenkomst tussen bijv. banaan en sinaasappel = fruit [ ] trein-fiets [ ] horloge-liniaal __/2

UITGESTELDE RECALL — Punten alleen voor recall zonder cue __/5

	Woorden moeten herinnerd worden **zonder cue**	GEZICHT [ ]	FLUWEEL [ ]	KERK [ ]	MADELIEF [ ]	ROOD [ ]
Optioneel	Categoriecue					
	Meerkeuzecue					

ORIËNTATIE [ ] Datum [ ] Maand [ ] Jaar [ ] Dag [ ] Locatie [ ] Plaats __/6

www.mocatest.org

Normaal ≥ 26 / 30

TOTAAL __/30

Tel er 1 pt bij op indien ≤ 12 jr opleiding

Appendix 4: Visual Analogue Scale (VAS) Freyd M (1923); Nederlandse versie, o.a.: van der Kloot WA, Vertommen H (1989)

Visual Analogue Scale (VAS)
Hayes & Patterson, 1921

Naam:	Geb. dat.:
Datum van afname:	

Wij willen u verzoeken dadelijk één vraag te beantwoorden waarmee we uw pijnintensiteit willen meten.

Plaats een verticale streep op de lijn die het best de ernst van uw pijn weergeeft.

Hoe hevig was uw pijn gemiddeld de afgelopen week (7 dagen)?

Geen enkele pijn (0 mm) _____ **Meest voorstelbare pijn (100 mm)**

Hoe hevig was uw pijn op de slechtste momenten in de afgelopen week (7 dagen)?

Geen enkele pijn (0 mm) _____ **Meest voorstelbare pijn (100 mm)**

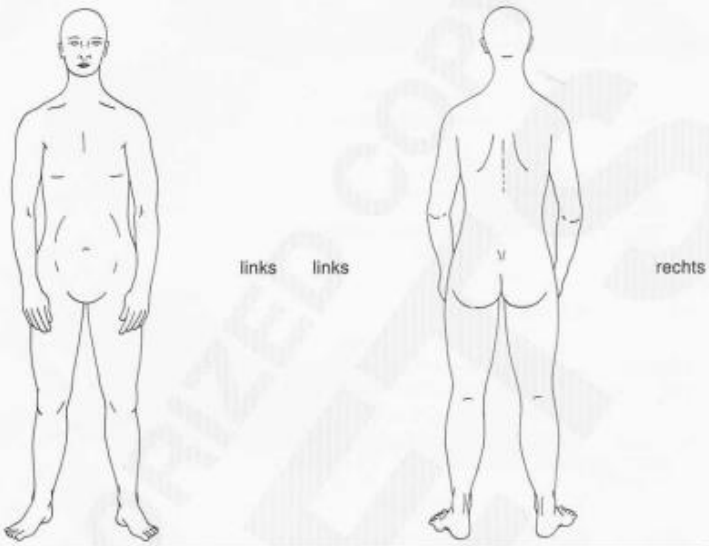
Toevoeging: Bij de scoring moet de VAS-lijn 10 cm lang zijn. De therapeut leest de score van de patiënt af met een liniaal.

Appendix 5: McGill Pain Questionnaire (MPQ) Melzack R (1975); Nederlandse versie: van der Kloot WA, Oostendorp RA (1995)

DE MPQ-DLV PIJNVRAGENLIJST

R. J. Verkes, K. Vanderiet, H. Vertommen, W. A. van der Kloot, J. van der Meij

Wilt U op onderstaande tekeningen aangeven waar U pijn hebt?



Hieronder en op de bladzijden hierna wordt een aantal vragen gesteld over de pijn waar U last van hebt. Als U op verschillende plaatsen pijn hebt, vult U de vragen dan in voor die pijn die het ergste is en waarvan U de meeste hinder ondervindt.

Hoelang hebt U last van deze pijn?
..... jaar
..... maanden
..... weken
..... dagen

Hoe is Uw pijn ontstaan? plotseling / geleidelijk

Zit Uw pijn steeds op dezelfde plaats(en)? ja / nee

Straalt Uw pijn uit naar andere plaats(en)? ja / nee

Schiet Uw pijn van de ene naar de andere plaats? ja / nee

Welk van de onderstaande uitspraken is het meest van toepassing op de pijn waarvan U last hebt? Kies één antwoord uit door een kruisje te zetten.

..... de pijn verloopt in aanvallen, d.w.z. tussen de aanvallen is de pijn weg.

..... de pijn is afwisselend van ernst maar is nooit helemaal weg.

..... de pijn is steeds even erg aanwezig.

SWETS TEST PUBLISHERS

03/1500.02

Appendix 6: Pain Assessment in Impaired Cognition (PAIC-15) Lautenbacher S, Achterberg W (2011); Nederlandse versie: van Dalen-Kok AH, et al. (2018)

Naam cliënt: Datum:

Pain Assessment in Impaired Cognition (PAIC 15)

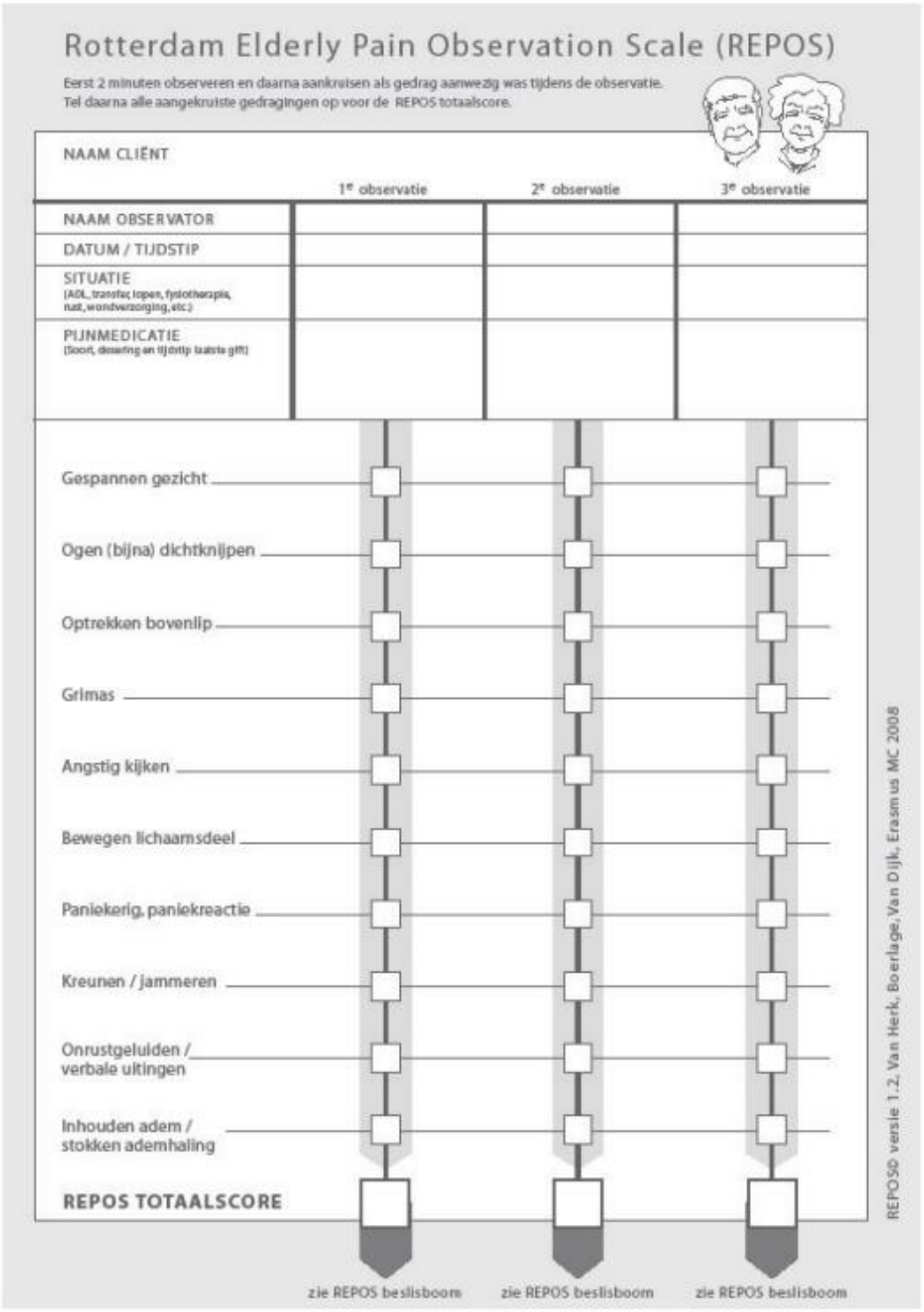
Item	Betekenis items	Helemaal niet	Geringe mate	Gemiddelde mate	Hoge mate	Niet scoobaar
GEZICHTSUITDRUKKINGEN						
Fronsen	Wenkbrauwen omlaag bewegen en samentrekken	**0**	**1**	**2**	**3**	x
Ogen vernauwen	Oogleden samenknijpen, met spanning rond de ogen	**0**	**1**	**2**	**3**	x
Bovenlip omhoog trekken	Bovenlip omhooggetrokken, huid rond neus kan plooien	**0**	**1**	**2**	**3**	x
Mond openen	Lippen en kaken van elkaar	**0**	**1**	**2**	**3**	x
Gespannen uitdrukking	Gezichtsuitdrukking is gespannen, bezorgd	**0**	**1**	**2**	**3**	x
LICHAAMSBEWEGINGEN						
Verstarren	Verstijving, vermijden van beweging, adem inhouden	**0**	**1**	**2**	**3**	x
Beschermen	Aangedaan lichaamsdeel beschermen, lichaamsdeel vasthouden, aanraking vermijden, afwenden	**0**	**1**	**2**	**3**	x
Verzetten tegen zorg	Verzetten tegen verplaatsing of zorg, niet meewerken	**0**	**1**	**2**	**3**	x
Wrijven	Aanraken of masseren van het aangedane lichaamsdeel	**0**	**1**	**2**	**3**	x
Rusteloosheid	Friemelen, in de handen knijpen, heen en weer wiegen	**0**	**1**	**2**	**3**	x
STEMGELUIDEN						
Pijngerelateerde woorden gebruiken	Pijnwoorden gebruiken zoals 'auw', 'ahh' of 'dat doet pijn'	**0**	**1**	**2**	**3**	x
Schreeuwen	Hard en/of hoog stemgeluid gebruiken om geluiden te uiten	**0**	**1**	**2**	**3**	x
Kreunen	Een laag, onsamenhangend geluid maken	**0**	**1**	**2**	**3**	x
Mompelen	Woorden en/of geluiden onduidelijk uitspreken	**0**	**1**	**2**	**3**	x
Klagen	Aangeven/zeggen ongelukkig, ziek of oncomfortabel te zijn en/of pijn te hebben	**0**	**1**	**2**	**3**	x
	Totaal =					

In welke situatie heb je de cliënt geobserveerd?

☐ Tijdens rust
☐ Tijdens algemene dagelijkse levensverrichtingen (ADL), namelijk:

☐ Tijdens een passieve beweging, namelijk:

Appendix 7 Rotterdam Elderly Pain Questionnaire Scale (REPOS) Van Herk, Boerlage, Van Dijk, Erasmus MC (2008)



Rotterdam Elderly Pain Observation Scale (REPOS)

Eerst 2 minuten observeren en daarna aankruisen als gedrag aanwezig was tijdens de observatie.
Tel daarna alle aangekruiste gedragingen op voor de REPOS totaalscore.

NAAM CLIËNT	1e observatie	2e observatie	3e observatie
NAAM OBSERVATOR			
DATUM / TIJDSTIP			
SITUATIE (ADL, transfer, lopen, fysiotherapie, rust, wondverzorging, etc.)			
PIJNMEDICATIE (Soort, dosering en tijdstip laatste gift)			

- Gespannen gezicht
- Ogen (bijna) dichtknijpen
- Optrekken bovenlip
- Grimas
- Angstig kijken
- Bewegen lichaamsdeel
- Paniekerig, paniekreactie
- Kreunen / jammeren
- Onrustgeluiden / verbale uitingen
- Inhouden adem / stokken ademhaling

REPOS TOTAALSCORE

zie REPOS beslisboom | zie REPOS beslisboom | zie REPOS beslisboom

REPOS© versie 1.2, Van Herk, Boerlage, Van Dijk, Erasmus MC 2008