The wave called delirium, from onset to consequences
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Chapter 9

General discussion
The focus of this thesis has been threefold. First, we investigated predisposing and precipitating risk factors for the development of delirium. Second, we focused on clinical symptomatology, namely duration and associated factors and motoric subtypes of delirium. The thesis concluded with studies of the (long-term) consequences of delirium, neuropsychological and affective functioning after delirium resolved. All these subject have been investigated in a relatively homogenous group, namely elderly hip surgery patients. The main advantage of such a patient group is that all patients experience the same sequence of events, and that they are relatively homogenous with respect to underlying illnesses compared to samples recruited from elderly patients acutely admitted to the hospital or patients from the ICU.

Another strength of this approach was that data on different clinical factors and demographics could be collected at baseline, so we were able to investigate (and thus to control for in our analyses) the relative importance of predisposing factors over precipitating events in delirium pathogenesis. It might be that these risk factors outweigh the impact of peri-operative events, such as anaesthetic technique.

**PART 1: ANESTHESIA AND INFLAMMATORY MARKERS FOR DELIRIUM**

Anesthetic technique has been suggested as precipitating factor for delirium. A theory is that the physiologic effects on cerebral blood flow, metabolism and oxygen delivery may differ between regional and general anesthesia, the latter having an increased risk of developing postoperative delirium. Also, the effects of drugs may be reduced or even eliminated with regional anesthesia. Results of previous studies are inconsistent, primarily due to the small number of patients included. A recent review concluded that postoperative delirium was not associated with anesthesia type, although a trend that postoperative cognitive dysfunction might be related to general anesthesia was found.¹

We were able to investigate the association between anaesthetic technique and postoperative delirium in a homogeneous group, controlling for other important delirium risk factors. Secondly, we investigated inflammatory markers before and after surgery. We compared CRP and levels between patients who developed postoperative delirium and patient who did not. Experimental findings and neuropathological observations suggest that activation of microglia is pivotal for mediation of the acute behavioural and cognitive effects of systemic inflammation.² A mild systemic inflammatory response suffices to increase the production of pro-inflammatory cytokines within the brain when microglia are already "primed" by chronic pathologic events as chronic neurodegeneration or advanced age.³ After hip surgery, the release of pro-inflammatory cytokines as a consequence of fracture and surgery induces a systemic inflammatory response. In older hip-fracture patients delirium was associated with higher postoperative serum levels of proinflammatory cytokines while no differences were seen in the preoperative serum levels between the delirium and non-delirium patients.⁴⁵
Anesthesia

In our relatively homogeneous hip fracture sample it was found that the risk of postoperative delirium was not increased in general anesthesia patients compared to patients receiving regional anesthesia. Patients with more baseline cognitive impairment, higher age, acute admission and other delirium risk factors present had also no association between anesthetic technique and postoperative delirium. The absence of a distinct association between general anesthesia and delirium is an important finding, especially that cognitively impaired patients were not at an increased risk of delirium after general anesthesia compared to regional anesthesia. Since this was not a randomized study, it remains possible that patients with intact cognitive function may have been more likely to be selected for regional rather than general anesthesia. However, baseline MMSE scores did not differ between the regional and anesthesia group, and we controlled for potential differences, such as MMSE score. We therefore believe that these findings do not reflect a referral bias to either general or regional anesthesia.

The use of narcotics, benzodiazepines and anticholinergic agents was not independently associated with delirium. We had to restrict analysis to these three well-known drug classes, because the study was underpowered to examine the effects of specific medications.

Studies examining effects of peri-operative drugs on postoperative delirium in hip-surgery patients are lacking. Exposure to benzodiazepine and opioid medication has been associated with increased delirium risk, but these findings must be interpreted with caution because of wide confidence intervals and different study populations. Impaired cholinergic function has been suggested as the common final pathway leading to delirium. We did find a higher percentage of patients receiving anticholinergics in the delirium group compared to non-delirium patients. However, this did not reach significance, which might represent a type II error due to our small sample size. Other classes of medication, particularly sedative-hypnotics and β-blockers may be associated with postoperative delirium. Although this study did not find an association between perioperative medication, anesthetic technique and postoperative delirium, it is difficult to reach a definitive conclusion on this subject. It might be that administered dosage is also of relevance to the risk of developing delirium, which we were unable to include in our analysis. Also, medication use postoperatively might be associated with postoperative delirium. Many other in-hospital events during surgery or not, might be of more importance than the anesthetic technique itself. A recent study found evidence that limiting sedation depth during spinal anesthesia decreases the prevalence of delirium. This indicates that other in-surgery factors might be associated with the risk for postoperative delirium and that they may be even more important than the anesthetic technique itself.
CRP
We found an increase in the level of inflammatory markers after surgery. The increase in the CRP level with patients who developed postoperative delirium was found after surgery and stayed higher in those patients who developed delirium postoperatively.

The pathogenic mechanisms underlying postoperative cognitive dysfunction remains unknown. It is suggested that the surgical trauma itself is mostly involved, more than perioperative factors such as hypoxaemia, hypotension or anesthesia. Surgical trauma has been associated with activation of the peripheral innate immune system, cytokine release and impairment of cognitive function. Several animal studies have shown that activation of the immune system, such as the stress response to surgery, results in an exaggerated inflammatory response in the hippocampus in aged organisms, which is followed by performance deficits in hippocampal-mediated cognitive tests in the aged animal compared to younger animals. In the aged organism, which is more vulnerable to impaired cognitive function after a peripheral immune challenge, this neuroinflammatory response can also be persistent.

We found that anaesthetic technique was not associated with the development of postoperative delirium. We did find an increase in the level of inflammatory markers after surgery and that a higher level of these markers is associated with postoperative delirium. This is in accordance with the suggestion that it is the surgical procedure itself, with the accompanying stress response, that is associated with the development of delirium.

PART 2: CLINICAL SYMPTOMATOLOGY
The second part of the thesis concerned the clinical symptomatology of delirium. Delirium duration is suggested to be associated with mortality risk and long-term cognitive impairment in ICU patients. A study in medical and surgical ICU survivors found that longer duration of delirium was associated with smaller brain volumes up to 3 months after discharge, and that smaller brain volumes are associated with long-term cognitive impairment up to 12 months. Persistent delirium has also been associated with more severe cognitive and non-cognitive disturbances compared to delirium that resolved over time. This was found in a study with palliative care patients with twice-weekly evaluations. We investigated if duration of delirium is associated with certain delirium symptoms (profile at onset and throughout) or clinical characteristics in a homogeneous group with data on daily evaluations of delirium symptoms.

One of the possible symptoms of delirium is an impaired motor function. Delirium was originally classified into two motor subtypes, i.e. hyperactive and hypoactive. A third category, mixed, was subsequently added in recognition that elements of both subtypes can appear within short time frames. The status of mixed motor subtype is still uncertain. Previous work with palliative care patients indicated that this subtype is common and associated with more severe overall delirium and stable over time in a
large percentage of patients. This supports mixed motor subtype as a separate motor category, and not just a reflection of the fluctuating nature of delirium or a transitional phase between hypoactive and hyperactive subtypes.

We investigated if different motoric subtypes are associated with specific characteristic and outcomes. Also, we investigated the stability of motor subtypes across the delirium episode, since there are little longitudinal data on motoric subtypes. We performed daily assessments of delirium, thus we could add to the existing longitudinal research to increase our understanding of the existence of different motor subtype categories. Since most studies are cross-sectional there is limited knowledge regarding the stability of motor subtypes over the course of delirium. Also, this study used a very active screening procedure, which reliably enabled to detect most if not all cases of delirium, including more easily missed hypoactive cases, which is a common problem in delirium research. This strengthens the reliability of the percentages of delirium motor subtypes found in our study.

Thereafter, we investigated the psychometric properties of the Delirium Motor Subtype Scale (DMSS), which we translated into Dutch. Previous subtyping methods have included behavioural abnormalities supposedly associated with motor activity levels, such as changes to affect, sleep, or psychotic symptoms. The DMSS combined features from three psychomotor subtyping schemas. Subsequently this was reduced to an 11-item Delirium Motor Subtype Scale (DMSS) based upon relative specificity of items for delirium vs. non-delirious controls and also according to correlation of items with independently assessed motor activity as per items 7 and 8 of the DRS-R98. This new tool emphasises disturbances of motor activity rather than associated psychomotor symptoms in motor subtyping.

**Delirium duration**

As a next step, we were interested in the predictive value of delirium symptomatology in the early phase of the delirium episode for its duration. In this thesis we used the duration of delirium in several analyses. For some analyses this implied we had to define the resolution of the delirium episode. We choose to consider 2 consecutive days of no delirium as recovery. This method is supported by a recent review of treatment for delirium, which considered available evidence for defining ‘recovery’. This review concluded that because of the fluctuating course of delirium, recovery is best defined conservatively and in the manner used in this thesis.

We found that the severity of individual delirium symptoms at the first day of delirium was not associated with short or prolonged delirium. Pre-existing cognitive impairment, which has repeatedly proven to be of importance in relation to delirium, was the only examined variable to be associated with prolonged delirium. The finding that cognition rather than delirium profile is associated with delirium duration is replicated twice within
this study with two independent methods. The GEE method is an innovative statistical analysis used for longitudinal data analysis, the small sample size is less important with this analysis because we have a relative large number of observations because of daily assessments.

The main finding in our study was that an association exists between prolonged delirium and pre-existent cognitive decline. It has been postulated that this reflects the effects of uncontrolled neuro-inflammation contributing to delirium symptoms. Since inflammatory markers have been shown to be elevated in dementia as well as MCI, it follows that pre-existent cognitive impairment might not only increases the chance of developing delirium, but also prolong the episode with delirium.

We found that almost half of the delirious patients experienced a delirium episode of 1 to 2 days. This short time-frame might suggest that this is of no relevance to the patients well-being or recovery. However, recent work has highlighted the impact of even short periods of delirium upon outcomes and therefore the importance of daily assessments in studies of delirium. Also delirium can be a very frightful experience, whether it lasts a day or a week.

**Motor subtypes: characteristics, outcomes and longitudinal stability**

Subtype categorization according to dominant motor subtype across the delirium episode identified groups that did not differ significantly in characteristics or outcomes. The evident similarity across the motor subtypes of this generally heterogeneous syndrome suggests the need to consider all therapeutic options relevant to delirium, regardless of motor presentation.

Notably, longitudinal assessment indicated that most patients had a variable course, with few patients having a consistent motor profile throughout their delirium episode. This challenges the validity of existing knowledge of motor subtypes which is almost exclusively derived from cross-sectional studies, limiting the distinction of the motor types if the majority of patients have variable motor subtypes across their delirium course as was evident in this study.

Relatively little is known about the longitudinal trajectory of motor subtypes in delirium. We investigated the longitudinal course of motor subtypes for each patient and found that many patients transitioned several times during the delirium episode with, for example, 87% changing motor subtype category between the first and second day of delirium. Previous longitudinal work in palliative care patients found that most patients (62%) had a stable pattern, with hypoactive subtype being the most common stable pattern (29%). The observed variability was related to the number of assessments, since patients with a variable subtype course had significantly more visits than the patients with a stable pattern. This pattern was also evident in the study reported herein where patients with more data showed a more variable pattern.
The unstable course of motor subtypes in our study might be associated with medication changes. However, the degree of variability was so marked that this factor alone is unlikely to fully account for the pattern and a previous study in palliative care patients using general estimating equations analysis found few associations existed between motor subtype (stable hypoactive, stable hyperactive, stable mixed, stable no subtype and variable course) and medication exposure or etiologies. Moreover, subtype transitions in the variable course group were rarely (14/102) preceded by a change to psychotropic medication apart from the finding that almost half of the transitions into the hypoactive subtype were preceded by increased benzodiazepine dosing. Further research is needed in populations other than palliative care patients to explore the stability of motor subtypes and to explore their relevance to other clinical characteristics and outcomes when longitudinal expression is considered.

**The Delirium Motor Subtype Scale (Dutch version)**

In Chapter 5 we used the DRS-R98 as a reference measure of motor activity to differentiate motor subtypes. The Dutch version of the DRS-R-98 has been found to distinguish hypoactive and non-hypoactive subtypes. However, this instrument is not developed specifically for motor subtype categorization and uncertainty remains about optimal cut-off scores. The Delirium Motor Subtype Scale (DMSS) is relatively more precise regarding the particular aspects of motor activity that can define subtypes and is also designed for use by a range of healthcare staff, rather than those with delirium-expertise as recommended for the DRS-R98. Therefore it was decided to translate the DMSS and examine psychometric properties of the Dutch version of the Delirium Motor Subtype Scale in our sample of hospitalized elderly hip-fracture patients with and without delirium. The Dutch DMSS had good agreement with the DRS-R98 on motor subtype identification, which confirms the findings in the initial study on the DMSS. In contrast to the DRS-R98 method of subtype attribution, the DMSS had greater specificity for delirium as evidenced by the substantially lower attribution of motor subtypes in non-delirious patients. However, it remains unclear whether the three motor subtypes represent distinct categories, since less significant differences have been found for the mixed subtype. Further research with the use of more ‘objective’ measures of motor activity, such as actigraphy / electronic motion analysis, and also categorization like the DMSS can advance our knowledge on this subject.

This study highlights that there is much lower concordance between the DMSS and DRS-R98 methods regarding the attribution of mixed rather than other clinical subtypes and suggests that its delineation may require further revision informed by studies in other clinical populations and using electronic motion analysis.

More than 90% of delirious patients met criteria for either hypoactive, hyperactive or mixed motor subtypes whilst in contrast 87% of non-delirious patients were deemed
‘no subtype’ emphasising the relative specificity of the motor activity items in the DMSS for delirium. This is in keeping with the method by which the DMSS items were selected i.e. according to relative specificity of motor symptoms for delirium vs. non-delirious controls.

**PART 3: THE CONSEQUENCES OF POSTOPERATIVE DELIRIUM: COGNITIVE AND AFFECTIVE FUNCTIONING**

Although delirium may resolve with time, it is suggested to be associated with long-term poor outcome. Delirium can contribute to poor cognitive and affective functioning, although not all research is consistent on this. Differences in results might be because of different patient populations, and the type of surgery or methodology.

Animal studies suggest that a temporal dissociation might exist between the acute behavioural changes and the depressive symptoms, which are based on distinct and time-related differences in the underlying biological mechanisms. In a study with elderly hip-fracture patients it has been found that depressive symptoms were associated with increased cytokine levels as long as at 1 year follow-up.

Also, subsyndromal delirium or persisting delirium might negatively effect cognitive functioning after 6 months. Depression might also effect cognition, so it is important to consider this interrelationships between affective and cognitive functioning when investigating the association between delirium and cognitive or affective functioning at follow-up.

**Cognitive functioning**

In Chapter 7 we evaluated cognitive performance, using a comprehensive neuropsychological approach, at follow-up in elderly hip fracture patients who did or did not suffer from in-hospital delirium. In-hospital delirium was found to be independently associated with impairments on tests of global cognition and episodic memory at follow-up. This result cannot be readily explained by persistent delirium or presence of depressive symptoms as we will discuss in the following section.

Patients with in-hospital delirium, but without delirium symptoms at follow-up (i.e. CAM score of null), performed worse on an episodic memory test than controls who never experienced delirium. Also, the persistence of delirium might affect cognitive outcome at follow-up in some patients, as almost 20% of our patients with in-hospital delirium was excluded because of persistent (or recurrent) delirium.

Another suggested explanation is that delirium may unmask early or prodromal dementia or may initiate or accelerate a process of cognitive decline. Many of the patients in our study who developed delirium showed signs of pre-fracture cognitive decline. Therefore, we controlled for baseline cognitive impairment in multivariate models. In addition we repeated analysis in subgroups of patients that did not show any sign of
cognitive impairment at baseline. Patients who had experienced in-hospital delirium still had a worse performance on a test which mainly measures episodic memory, compared to controls.

Delirium has been associated with higher depressive symptom levels months after hip fracture, and depression can markedly affect cognitive function. Therefore, we repeated the analysis in patients with few or no depressive symptoms present at follow-up. In-hospital delirium remained associated with poorer performance on a range of neuropsychological tests. Also, delirium patients in our study showed disproportionate memory disturbances, in contrast to diminished processing speed and impaired executive function, which is more characteristic of depression in late life. These results suggest that an increase of depressive symptoms at follow-up among patients with previous delirium cannot fully explain their poorer cognitive functioning. To date few if any studies have examined the association between delirium and cognitive impairment at follow-up while simultaneously documenting the presence of mood disturbances.

**Affective functioning**

In addition to the cognitive functioning at follow-up in the previous study, we examined the association between in-hospital delirium and affective functioning three months after hospital discharge. The occurrence of in-hospital delirium was independently associated with increased depressive symptoms 3 months after hospital discharge, whereas no association was found for anxiety levels or posttraumatic stress symptoms.

We found that patients with in-hospital delirium have increased depressive symptoms three months later, in the absence of (sub)syndromal delirium. So, increased depressive symptoms after a delirious episode can not readily be explained by prolonged delirium or (sub)syndromal delirium.

An explanation for the increase in depressive symptoms after in-hospital delirium in elderly patients could be underlying cognitive impairment. Depression and dementia are suggested to be related, with increased prevalence of depression in people suffering from dementia. People with delirium were more cognitively impaired at baseline and were still more cognitively impaired three months after hospital discharge. This is why we controlled for baseline cognitive functioning in multivariate analysis, in-hospital delirium was still associated with more depressive symptoms at follow-up. In a subsample of patients without evidence of cognitive impairment at baseline (MMSE>23 and IQCODE-N<3.6) again that patients with in-hospital delirium had more depressive symptoms at follow-up compared to controls.

In the present study no difference was found in anxiety levels between patients with and without in-hospital delirium three months after hospital discharge. However, anxiety levels did increase in both the delirious and control group. This might be related to the effects of hospitalization and having experienced surgery and interventions. The present
study did not find an association between in-hospital delirium and PTSD symptoms at follow-up. It has been suggested that higher levels of PTSD symptoms are less likely to occur in older patients, as we found in our study.57

Final concluding words
This thesis investigated predisposing and precipitating risk factors for the development of delirium. The second part of this thesis focused on clinical symptomatology, namely duration and associated factors and motoric subtypes of delirium. The final part investigated the neuropsychological and affective functioning after postoperative delirium.

The strengths of our study are that we used a homogenous population, with baseline data available from the period before surgery and onset of delirium. This enabled us to investigate the (inter)relationship between development of delirium and predisposing factors, such as cognition and comorbidities, clinical characteristics and outcomes at a three month follow-up.

Except for chapter 2 on anesthesia, all other studies were part of a randomized controlled trial comparing the effectiveness of taurine versus placebo in reducing morbidity and one-year mortality. This might be considered a weakness of our study. However, we routinely controlled for treatment modality, and this did not affect the results in any of our analyses.

All the patients in our sample who were at high-risk of delirium received haloperidol prophylaxis. Haloperidol might have had an effect on motor symptom profile, but similar longitudinal work in a palliative care setting suggests a limited relationship between motor activity and use of antipsychotic agents.58 Also, if any effect existed, it will have been for all the patients in our sample and not a subgroup.

This thesis investigated several aspects of delirium, from onset to outcomes. It focused on interactions between different factors and their association with delirium. It is important to unravel the underlying mechanisms and further improve prevention and therapeutic interventions, both in the acute phase and in the long term. Although it has been suggested that general anaesthesia increases the risk at delirium, we did not find an indication for this. Recently, it has been hypothesized that neuroinflammation might induce delirium, especially in individuals who are predisposed to develop delirium59,60 and it might also have a role in the development of depression and cognition afterwards.61 The role of inflammation and other suggested mechanisms need further exploration in future research.
REFERENCES


