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Thinking through postoperative cognitive dysfunction: How to bridge the gap between clinical and pre-clinical perspectives

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ABSTRACT

Following surgery, patients may experience cognitive decline, which can seriously reduce quality of life. This postoperative cognitive dysfunction (POCD) is mainly seen in the elderly and is thought to be mediated by surgery-induced inflammatory reactions. Clinical studies tend to define POCD as a persisting, generalised decline in cognition, without specifying which cognitive functions are impaired. Pre-clinical research mainly describes early hippocampal dysfunction as a consequence of surgery-induced neuroinflammation. These different approaches to study POCD impede translation between clinical and pre-clinical research outcomes and may hamper the development of appropriate interventions.

This article analyses which cognitive domains deteriorate after surgery and which brain areas might be involved. The most important outcomes are: (1) POCD encompasses a wide range of cognitive impairments; (2) POCD affects larger areas of the brain; and (3) individual variation in the vulnerability of neuronal networks to neuroinflammatory mechanisms may determine if and how POCD manifests itself.

We argue that, for pre-clinical and clinical research of POCD to advance, the effects of surgery on various cognitive functions and brain areas should be studied. Moreover, in addition to general characteristics, research should take inter-relationships between cognitive complaints and physical and mental characteristics into account.

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1. Introduction

Old age comes with infirmities, many of which can be successfully treated with surgery. Unfortunately, persistent cognitive impairments can develop as a side-effect of these surgical procedures, a phenomenon that is predominantly seen in the elderly (Krenk et al., 2010; Rasmussen, 2006). This complication has been termed 'postoperative cognitive dysfunction' (POCD). Surgery-induced cognitive decline leads to an increased risk of disability and mortality (Price et al., 2008; Steinmetz et al., 2009). As a consequence, patients can lose their employment or independence, which seriously reduces their quality of life (Dijkstra and Jolles, 2002; Monk et al., 2008; Price et al., 2008; Steinmetz et al., 2009). In view of the growing number of elderly, POCD constitutes not only a burden at the individual level, but also for society as a whole (United Nations, 2010).

There is currently no adequate treatment for POCD. Several animal models have been developed to study the underlying mechanisms and to find potential targets to treat or prevent cognitive impairments after surgery. However, it can be questioned whether the outcomes of these pre-clinical studies can be translated into clinical practise. In this review article, a critical comparison is made between the current clinical and pre-clinical views on POCD to indicate the translational gaps between these research fields. Based on an analysis of the cognitive domains and brain areas involved in this condition, suggestions are made to improve research on POCD.

2. Definition

In clinical studies of cognitive changes after surgery a distinction is made between delirium and POCD. Delirium is characterised as an acute and transient disturbance of mental functions that may be accompanied by changes in awareness (Funder et al., 2010; Krenk et al., 2010). POCD encompasses more subtle cognitive changes that are long lasting (Krenk et al., 2010). A second distinction that has been made is the occurrence of cognitive impairments

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after cardiac and non-cardiac surgery, since such impairments occur much more frequently after cardiac surgery (Rasmussen, 2006). It can be questioned whether these distinctions are relevant in terms of underlying pathology or if they are just different manifestations of one and the same process. Persistence of delirium symptoms, for example, has been reported several times (National Clinical Guideline Centre, 2010). For the purpose of this review, however, we will limit our definition of POCD to persistent cognitive impairments after non-cardiac surgery. We consider cognitive impairments to be persistent when they last for more than one week after surgery, in contrast to early declines in cognition, which occur within the first week.

3. Current views on POCD

Research into POCD can be divided into two distinct fields. Clinical research has mainly focused on determining the prevalence, risk factors and consequences of POCD. Conversely, pre-clinical studies have mainly investigated the mechanisms underlying POCD. Interestingly, these two fields seem to have developed in different directions.

3.1. The clinical perspective: diagnosis, incidence rate and risk factors

As early as 1955, Bedford described the occurrence of persistent cognitive impairments after non-cardiac surgery (Bedford, 1955). In the decades that followed, many studies were devoted to proving that this phenomenon indeed existed, but with limited results (Dijkstra and Jolles, 2002; Newman et al., 2007). During the same period, cognitive decline after cardiac surgery was proven (Newman et al., 2007). The difficulties of verifying POCD after non-cardiac surgery can be ascribed, on the one hand, to the relatively low incidence and, on the other hand, a lack of consensus regarding the definition of POCD and the use of insensitive test batteries (Rasmussen et al., 2001; Dijkstra and Jolles, 2002; Funder et al., 2010).

A change came in the mid-1990s when researchers started to define POCD as a decline in performance on at least two or three tests in a sensitive test battery following surgery (Moller et al., 1998; Steinmetz et al., 2009; Williams-Russo et al., 1995). Using this method, persistent cognitive decline could be demonstrated after non-cardiac surgery, although reported incidences of POCD still vary substantially, depending on the patient population, time of measurement and the neuropsychological tests used (Deiner and Silverstein, 2009; Rasmussen, 2006). In the International Study of POCD, which included more than 1,200 patients, a 10% incidence of POCD was observed in the elderly three months after surgery (Monk et al., 2008). In addition, risk factors for POCD, such as advancing age, the severity of surgery, the duration of anaesthesia, the occurrence of complications, pre-existing cognitive impairments and the level of education, have been determined (Moller et al., 1998; Monk et al., 2008; Price et al., 2008). As a consequence of these developments, clinical research usually defines POCD as persistent cognitive decline in one or more cognitive domains, without specifying what these domains are.

The cognitive domains that are said to be affected by surgery are memory, attention and information processing (Dijkstra and Jolles, 2002; Hanning, 2005; Krenk et al., 2010; Terrando et al., 2011). It is, however, unclear on what evidence this statement is based, since a detailed analysis of the neuropsychological test outcomes of patients with POCD has not yet been performed. To our knowledge, until now only four studies have made distinctions between the cognitive domains affected after surgery (Ancelin et al., 2001; Bekker et al., 2010; Hudetz et al., 2011; Price et al., 2008). Of these studies, only Hudetz et al. (2011) discussed, in more detail,

which functions and brain structures might be involved in POCD. Postoperative impairments were found in both executive function and recent memory, but were most pronounced in the latter modality. The authors noted that this might point towards involvement of several temporal and prefrontal brain structures. However, this study specifically focussed on patients with metabolic syndrome, so the results cannot be generalised to all patient categories. In addition, only tests of recent memory and executive functions were included in this study, so it remains uncertain what other cognitive functions are vulnerable to postoperative decline.

In conclusion, clinical research has led to a definition of POCD which facilitates diagnosis and determination of the incidence rate and risk factors of this condition, while an analysis of the symptoms has been overlooked.

3.2. The pre-clinical perspective; mechanism

Several mechanisms have been proposed to be involved in the development of cognitive impairments after surgery, including changes in cerebral blood flow, sleep disturbances, effects of anaesthetics, and inflammation. Hypoperfusion, hypoxia and the formation of micro-emboli have been shown to occur during and after surgery, and could potentially cause ischaemic brain damage, but a clear relationship with POCD has not been found (Krenk et al., 2010). Sleep disturbances can occur after surgery or due to the use of medication, such as opioids, and are known to affect cognitive performance (Krenk et al., 2010), but research on the influence of such disturbances on POCD is scarce and inconclusive (Gögenur, 2010). Some types of anaesthesia have been shown to cause neurodegenerative changes in animal studies (Culley et al., 2004; Kalenka et al., 2010; Papaioannou et al., 2005). However, numerous studies investigating the relationship between POCD and anaesthesia have consistently failed to find a relationship (Cao et al., 2010; Cibelli et al., 2010; Krenk et al., 2010; Newman et al., 2007; Rosczyk et al., 2008).

Consistent evidence is accumulating only for the role of inflammatory processes arising due to surgical trauma and subsequent complications. Where clinical studies have provided leads to the understanding of this mechanism, most of the studies researching the mechanism in more detail have been performed using animal models. Although low levels of immune activation are necessary for regulating normal cognitive functions, the high levels of pro-inflammatory factors associated with trauma or infection, have been shown to detrimentally affect cognitive processes (Yirmiya and Goshen, 2011). In patient studies, it was shown that tissue damage associated with surgery activates the peripheral innate immune system, leading to the release of inflammatory mediators such as cytokines, reactive oxygen species and endothelins (Giannoudis et al., 2006; Karlidag et al., 2006; Levy and Tanaka, 2003). These increases in peripheral levels of inflammatory factors after surgery, such as IL-6 and IL-1 β , have been related to a decline in cognitive performance (Beloosesky et al., 2007; Cibelli et al., 2010; Ramlawi et al., 2006; Yaffe et al., 2003). More evidence comes from the finding that the risk of cognitive decline increases with increased surgical severity and the occurrence of complications, as both of these factors are related to a higher magnitude of the inflammatory response (Cibelli et al., 2010; Krenk et al., 2010; Maze et al., 2008; Xie et al., 2009; Zakzanis et al., 2005). In accordance with these findings, a study by Fidalgo et al. (2011a) showed that sub-clinical inflammation following administration of lipopolysaccharide substantially increased IL-1 β plasma levels and cognitive deterioration after surgery.

Once released into the systemic circulation, inflammatory mediators can exert effects in the central nervous system (CNS) via several routes. First, cytokines, such as IL-1, IL-6 and TNF α , can cross the blood brain barrier (BBB) through the relatively

permeable periventricular regions or by active transport (Galea et al., 2007; Dilger and Johnson, 2008). Second, cytokines can bind to receptors on the endothelial cells of the BBB, which leads to the secretion of inflammatory factors in the CNS (Dilger and Johnson, 2008). Finally, vagal afferent nerves can rapidly activate central inflammatory pathways, when stimulated by immune factors in the periphery (Dilger and Johnson, 2008; Maier, 2003). All of these pathways together lead to activation of microglia in the CNS, which, in turn, produce cytokines, reactive oxygen species and other inflammatory factors (Lucin and Wyss-Coray, 2009; Schiepers et al., 2005). In accordance with these findings surgery was associated with microglia activation that lasted up to three days after surgery (Cao et al., 2010; Cibelli et al., 2010; Wan et al., 2007), as well as hippocampal increases in the expression of IL-1 β and IL-6 (Cao et al., 2010; Cibelli et al., 2010; Fidalgo et al., 2011a, 2011b; Rosczyk et al., 2008; Tan et al., 2010; Wan et al., 2010).

Elevated cytokine levels are thought to influence neuronal processes either directly or through interactions with neurotrophins and neurotransmitter systems (Yirmiya and Goshen, 2011). Fidalgo et al. (2011b), for example, showed that increases in hippocampal IL-1 β after orthopaedic surgery coincided with a reduction in brain-derived neurotrophic factor. Furthermore, as illustrated by Tan et al. (2010), increased cytokine levels after surgery may cause tau hyper-phosphorylation and the formation of the neurofibrillary tangles associated with Alzheimer's disease. Whether these changes are serious enough to elicit neurodegeneration, or cause a more subtle change in neuronal function, remains to be determined.

The hippocampus seems especially vulnerable to the inflammation-mediated changes described above (Yirmiya and Goshen, 2011). Consequently, pre-clinical studies have mainly focused on the role of inflammation in the surgery-induced decline of hippocampal function. These studies have used contextual fear memory (Cibelli et al., 2010; Terrando et al., 2010; Fidalgo et al., 2011a, 2011b), spatial learning (Wan et al., 2007, 2010; Tan et al., 2010; Wuri et al., 2011) or reversal learning (Rosczyk et al., 2008; Cao et al., 2010) to demonstrate post-surgical impairment in hippocampus-mediated cognition that coincided with hippocampal inflammatory changes. Only Cibelli et al. (2010) investigated the effect of surgery on non-hippocampal memory, measured using auditory fear conditioning. They did not find any differences between animals that underwent surgery or animals that served as control. These results are consistent with previous studies that showed a negative influence of pro-inflammatory cytokines on contextual, but not auditory-cued, fear conditioning (Yirmiya and Goshen, 2011).

In line with most research on cytokine-induced cognitive changes, pre-clinical studies tend to investigate cognitive decline early after surgery and in young animals (Cao et al., 2010; Cibelli et al., 2010; Fidalgo et al., 2011a; Terrando et al., 2010; Wan et al., 2007). In these studies, cognitive and inflammatory changes seem to recede within one week after surgery, making it questionable whether the results truly reflect the persisting cognitive impairments of POCD in the elderly.

In conclusion, pre-clinical research has led to animal models, in which inflammatory mechanisms can indeed be related to reduced cognitive performance after surgery, but whether these models represent the specific characteristics of POCD in humans remains unclear.

4. Translational gap in POCD research

Summarizing the above, it can be said that whereas clinical research tends to define POCD as a persisting generalised decline in

cognitive functions, pre-clinical research mainly describes early inflammation-induced hippocampal dysfunction after surgery. This has led to a translational gap in the research on POCD which might lead to incomplete or incorrect assumptions about the underlying mechanisms and, as such, seriously hamper the development of appropriate therapies.

The translation of clinical findings to an animal model is hindered by the lack of a detailed analysis of the cognitive functions that deteriorate after surgery, since the rationale on which to base pre-clinical models for POCD is lacking. Moreover, by overlooking the type of cognitive decline after surgery, information is lost that could be used to gain insight into the underlying mechanisms.

At the same time, the absence of an animal model that includes all aspects of POCD impedes the translation of pre-clinical findings to the clinical setting. Even though, for example, POCD is considered a condition that persists for weeks or months after surgery, thus far only two animal studies (Fidalgo et al., 2011b; Wuri et al., 2011) have investigated persisting cognitive impairment after surgery. Only when consistency between clinical and pre-clinical research exists, can the mechanisms underlying POCD be truly understood and appropriate therapies developed.

5. Bridging the translational gap

In view of the fact that adequate therapeutic strategies against POCD need to be developed, the discrepancies between clinical and pre-clinical research in this field should be overcome. As noted above, the rationale for a good pre-clinical model of POCD is hampered by the lack of knowledge of the specific cognitive functions that deteriorate after surgery. The translation from the clinical to pre-clinical setting could be aided by analysing which cognitive functions deteriorate after surgery and which brain areas are involved in this deterioration. To this end, we performed two systematic searches (Supplementary data 1 and 2). First, we reviewed and analysed the clinical literature to determine which neuropsychological tests were used to study POCD (patient characteristics and methods used are presented in Tables 1 and 2 respectively) and which specific cognitive domains are affected in POCD (Table 3). Second, we investigated which brain areas are involved (Table 4). Based on these reviews we investigated the role of individual variation in the development of POCD.

5.1. Cognitive functions affected in POCD

The early and late decline in test performances of patients after surgery (Table 3) follow a similar pattern, although cognitive impairments are reported in a higher percentage of patients early after surgery. This might reflect the presence of delirium or delirium-related symptoms early after surgery. Memory functions, especially visual and verbal recall, seem to be affected in the highest number of patients. Price et al. (2008) and Hudetz et al. (2011) already noted this, based on the outcomes of their separate studies. Language and visuospatial processing also decline in a relatively large percentage of patients after surgery, with up to 15% of patients experiencing a decline in performance.

The cognitive functions that constitute the attention domain are affected in a smaller percentage of patients. It is therefore possible that this reported decline in attention is a consequence of natural variation in test performance. However, the attention impairments are consistently present in a number of tests and studies. Furthermore, concentration problems are frequently mentioned by patients after surgery (Debess et al., 2009; Dijkstra and Jolles, 2002; Jones et al., 1990). It has been argued that cognitive complaints after surgery do not correlate well with objective measurements of POCD (e.g. neuropsychological test outcomes). These complaints

Table 1

Systematic review of postoperative decline after non-cardiac surgery in humans: patient characteristics.

Author	Patients/controls (n)	% Male	Age (yrs.)	Type of surgery
Williams-Russo et al. (1995)	262	30	>40	Total knee
Grichnik et al. (1999)	29	65.5	35–85	Thoracic and vascular
Ancelin et al. (2001)	140	33	64–87	Orthopaedic
Iohom et al. (2004)	40/13	55	40–84	Cholecystectomy
Rodriguez et al. (2005)	29	46	45–82	Total knee
Silverstein et al. (2007)	1185 (74 PCI)/176	54	>60	Major surgery
Price et al. (2008)	334/62	57	>60	Major surgery
Steinmetz et al. (2009)	701	43	>40	Mixed surgery
Steinmetz et al. (2010)	70	37	61–83	Mixed surgery
Hudetz et al. (2011)	60 (30 METS)	0	≥55	Mixed surgery
Evered et al. (2011)	664 /34	61	>50	Total hip

PCI = pre-operative cognitive impairment; METS = metabolic syndrome; total knee = total knee arthroplasty; total hip = total hip joint replacement.

Table 2

Systematic review of postoperative decline after non-cardiac surgery in humans: methodology and incidence.

Author	Pre-op	Post-op	Test domains	Criteria POCD	Early decline	Late decline
Williams-Russo et al. (1995)	Yes	1 week 6 months	Memory (1,4,6,11,12) Attention (2) Information (I & L1, 2)	Decline > CID in > 3 tests	–	5%
Grichnik et al. (1999)	Yes	6– 12 weeks	Memory (2,3,6,8,9,10) Attention (2)	>20% decline in > 20% tests	–	44%
Ancelin et al. (2001)	Yes	9 days 3 months	Memory (13–15) Attention (4) Information (L3,4 & V2,3)	Decline > 1SD 1 or more scores	–	70% (9d) 66% (6–12w)
Iohom et al. (2004)	Yes	4 days 6 weeks	Memory (8) Attention (1,2) Information (I & L1)	RCI deficit in one or more tests	40%	53%
Rodriguez et al. (2005)	Yes	1 week 3 months	Memory (6,11) Attention (1,2) Information (V1& L1,2)	Decline of > 0.5 SD in > 20% tests	41%	18%
Silverstein et al. (2007)	Yes	7 days 3 months	Memory (7) Attention (1,3) Information (I)	2 Z scores or combined Z score > 1.96	19% PCI 26% no PCI	15% PCI 10% no PCI
Price et al., 2008	Yes	7 days 3 months	Memory (7) Attention (1,3) Information (I)	RCI deficit in one or more tests	23% executive 18% memory 15% combined	8% executive 14% memory 3% combined
Steinmetz et al., 2009	Yes	7 days 3 months	Memory (7) Attention (1,3) Information (I)	2 Z scores or combined Z score > 1.96	20%	10%
Steinmetz et al., 2010	Yes	7 days	Memory (7) Attention (1,3) Information (I)	2 Z scores or combined Z score > 1.96	14%	–
Hudetz et al., 2011	Yes	1 month	Memory (3,4, 5,10,11,12) Attention (1) Information (L2)	2 Z scores or combined Z score < - 1.96	–	43% METS 27% no METS
Evered et al., 2011	Yes	7 days 3 months	Memory (7) Attention (1,3) Information processing (I)	2 RCI scores or combined Z score < - 1.96	17%	16%

The tests are coded on the basis of [Supplementary data 3](#). PCI = pre-operative cognitive impairment; METS = metabolic syndrome; CID = clinically important difference; RCI = reliable change index.

have been said to depend more on mood and the patient's notion of cognitive impairment (Debess et al., 2009; Dijkstra and Jolles, 2002). However, cognitive tests are usually performed in a controlled environment. It could be that only a substantial impairment of information processing and attention leads to a decline in test performance under these circumstances. Perhaps patients with limited impairment only experience these problems when they have to sustain their attention over a longer period of time combined with a lot of interference, as occurs in daily life. Therefore, it cannot be excluded that at least a some POCD patients experience attention problems. Processing speed is decreased in a very small percentage of patients (1–3%) on the long term (Iohom et al., 2004; Price et al., 2008; Silverstein et al., 2007; Williams-Russo et al., 1995). This could be due to the relatively simple character of these tests.

The large methodological differences in patient characteristics (Table 1) and methods to determine POCD (Table 2) lead to diverse study outcomes. Although this could hamper a clear interpretation of the results, the diversity is informative in itself. It can be inferred that working memory, encoding and retrieval of long-term memory, information processing, processing speed, selective attention, attention shifting and mental flexibility are all sensitive to persisting postoperative decline. The problems experienced by POCD pa-

tients are thus not limited to one cognitive domain but are present over several cognitive functions.

5.2. Brain areas involved in POCD

Table 4 gives an overview of the brain regions involved in the cognitive functions that may decline after surgery, based on human imaging studies. The areas possibly involved in POCD include pre-frontal, frontal, parietal, temporal, occipital, hippocampal, insular, cingulate, thalamic and cerebellar regions. Most of these brain areas are not specifically activated in one cognitive function but are involved in several functions. For example, the dorsolateral prefrontal cortex and posterior parietal cortex seem to be involved in almost all of the neurocognitive domains that are discussed in this article. An impairment in one of the areas generally involved in cognitive functioning, could cause the decline in all domains. However, considering the current hypothesis that neuroinflammation is involved in POCD development, it is more likely that these impairments are not restricted to one brain area, but affect more areas, or even the whole brain. Increased levels of inflammatory factors play a role in diseases related to a range of brain areas and structures (Lucas et al., 2006). Moreover, animal studies have repeatedly shown neuroinflammatory changes in the hippocampus

Table 3

Summary of the cognitive domains and relevant neuropsychological tests that were used to study postoperative cognitive decline after non-cardiac surgery in humans.

Domain	Tests	Early decline	Late decline
<i>Memory (M)</i>			
Working memory	Digit span	15% ^a	8–25% ^{a,b,c}
Encoding and retrieval of long-term memory	Verbal and visual recall and recognition	5–39% ^{a,b,c,d,e,f,g,h}	1–30% ^{a,b,c,e,f,g,h,i,j}
<i>Attention (A)</i>			
Mental flexibility	Trail Making Test	4–10% ^{a,b,d,e,g,j}	3–16% ^{a,b,d,e,f,j,k}
Selective attention	Stroop test	10–15% ^{e,h,j}	5–6% ^{c,g,h,j}
General	ECO attention, WMS-R	No ^g	No/Yes ^{g,i}
<i>Information processing</i>			
Information processing (I)	Substitution test	8–14% ^{a,e,f,h,j}	1–3% ^{a,e,f,h,j,k}
Language processing (L)		4%–15% ^{a,f,g}	1–15% ^{a,f,g,i,k}
Visuospatial processing (V)		12–25% ^f	3–19% ^{f,i}

The tests have been divided in cognitive domains. These are memory, attention and information processing. The tests that address memory focus on: (1) working memory: the retention and manipulation of small amounts of information for a short period of time (Baddely et al., 2009; Friedenberg and Silverman, 2006); or (2) long term memory: encoding and retrieval of information over longer periods of time. The tests that address attention can be divided into tests that measure: (1) mental flexibility: the ability to shift between tasks or strategies (Moll et al., 2002; Mrak, 2009; Wager et al., 2004; Zakzanis et al., 2005); or (2) selective attention: the ability to selectively focus on that part of the information that is of importance (Leung et al., 2000; Liotti et al., 2000). Information processing tasks focus on: (1) processing speed: the speed of perception and information processing (Usui et al., 2009); (2) language processing: the ability to comprehend and form spoken language; or (3) visuospatial processing: the ability to analyse and organise visual stimuli.

^a (Williams-Russo et al., 1995).

^b (Crichnik et al., 1999).

^c (Hudetz et al., 2011).

^d (Steinmetz et al., 2010).

^e (Price et al., 2008).

^f (Iohom et al., 2004).

^g (Rodriguez et al., 2005).

^h (Silverstein et al., 2007).

ⁱ (Ancelin et al., 2001).

^j (Steinmetz et al., 2009).

^k (Evered et al., 2011).

after surgery (Cao et al., 2010; Cibelli et al., 2010; Fidalgo et al., 2011a, 2011b; Rosczyk et al., 2008; Terrando et al., 2010; Wan et al., 2007, 2010). It seems improbable that changes in hippocampal function alone are responsible for all cognitive impairments seen after surgery (Table 4).

In summary, various brain areas are involved in the neurocognitive functions that deteriorate in POCD. It seems that the mechanisms behind POCD affect the brain in general and this leads to impairments in several cognitive domains.

5.3. Inter-individual variation in POCD development

Large inter-individual differences between patients can be observed in neuropsychological test outcomes after surgery. For every test there is a small percentage of patients who show a decline in performance, but usually it is not the same patient that shows a decline on every test. Ancelin et al. (2001), for example, found that nine days after surgery, 71% of the patients showed impairments in any combination of the performed tests, while on each separate test, a maximum of only 45% of the patients showed a decline. Conversely, the study by Williams-Russo et al. (1995) showed that, six months post-surgery, only 5% of all patients experienced a persisting decline on three or more tests, while on each separate test, there was a considerably higher percentage of patients that declined in performance. These studies exemplify the individual variability in cognitive tasks that are affected by POCD. This phenomenon is further illustrated by a study by Price et al. (2008). They made a distinction between patients that experienced impairments in memory function, in executive function or in both these functions. Of the patients in this study, 14% showed only memory decline, 8% showed only a decline in executive function, and 3% showed a dysfunction in both memory and executive function three months after surgery. These results indicate that the clinical manifestation of POCD can vary widely between individuals and is likely to depend on individual characteristics.

6. Potential mechanisms underlying inter-individual variation

Many mechanisms can potentially increase one's vulnerability to cognitive deterioration, such as variations in the genetic code, metabolic and cardiovascular functioning. Since evidence points towards an inflammatory mechanism underlying POCD, it is interesting to consider whether variations in vulnerability to such an inflammatory mechanism can influence POCD manifestation.

Old age is considered the most important risk factor for POCD (Dijkstra and Jolles, 2002; Moller et al., 1998; Newman et al., 2007; Price et al., 2008). Investigating why the elderly are at greater risk of developing POCD can lead to more insight into factors that determine the individual vulnerability to this condition. Neuroinflammatory priming and existing neuron degeneration are two of these factors.

6.1. Vulnerability to neuroinflammation

With ageing, changes occur in the mechanisms regulating the inflammatory processes in the brain. Ageing has been associated with microglial priming in rodents and humans (Dilger and Johnson, 2008; Frank et al., 2010; Wynne et al., 2009). Under basal conditions primed microglia cells secrete minimal amounts of cytokines. However, they are hyper-responsive to secondary stimuli and display an increased and prolonged production of inflammatory factors when activated (Combrinck et al., 2002; Wynne et al., 2009; Frank et al., 2010). Furthermore, an increased permeability of the BBB has been reported in aged humans as well as animal models of senescence (Popescu et al., 2009). These processes make the aged brain both more susceptible and more reactive to cytokines from the periphery, leading to an exacerbated neuroinflammatory response and, consequently, a higher risk of memory impairment (Dilger and Johnson, 2008; Lucin and Wyss-Coray, 2009; Sparkman and Johnson, 2008). Barrientos and colleagues (Barrientos et al., 2006, 2009) illustrated this by injecting adult and aged rats with *Escherichia coli*. The aged animals displayed

Table 4
Brain areas involved in cognitive functions.

Area	Specific location	Working memory	Long-term memory	Mental flexibility	Selective attention	Processing speed	Language processing	Visual processing
Prefrontal	Dorsolateral	x	x	x	x	x		
	Ventrolateral	x		x				
frontal	Inferior		x					
	cortex (general)		x		x	x		
	Premotor	x						
	Inferior				x	x		
Parietal	Cortex (general)			x	x	x		
	left Posterior cortex	x	x	x	x	x	x	
	right posterior cortex	x	x	x	x	x		x
	Broca's area		x	x			x	
	Wernicke's area						x	
Occipital	Cortex (general)			x		x		x
Temporal	Cortex (general)			x	x		x	x
	Inferior		x					
Hippocampus			x					
Cingulate	Anterior	x	x	x	x			
Insula				x	x			
Thalamus			x					
Cerebellum			x					
Schematic representation of brain areas involved in cognitive functions

The cognitive functions that seem to be affected in POCD are shown. The two left columns show the brain areas and the specific locations in these areas that have been found to be involved in these functions. A schematic visual representation is added of the general brain areas that are involved in each cognitive function, based on our literature review. (Andreasen et al., 1995a,b,c; Baddely et al., 2009; Brand and Jolles, 1985; Buckner et al., 1998; Dickerson et al., 2007; Forn et al., 2009; Friedenberg and Silverman, 2006; Gazzaniga et al., 2002; Leung et al., 2000; Liotti et al., 2000; MacDonald et al., 2000; MacLeod and MacDonald, 2000; Moll et al., 2002; Monchi et al., 2001; Paulesu et al., 1993; Owen et al., 2005; Smith et al., 1996; Smith and Jonides, 1997; Squire, 1992; Staresina and Davachi, 2006; Sylvester et al., 2003; Usui et al., 2009; Wager et al., 2004; West and Alain, 1999; Williams-Russo et al., 1995; Zakzanis et al., 2005).

an exaggerated and prolonged increase in IL-1 β levels that was associated with increased memory impairment when compared to young rats. Similarly, it was shown that in aged versus young rodents, surgery leads to increases in microglial activation, IL-1 β levels and IL-6 levels, contributing to a decline in cognitive flexibility (Rosczyk et al., 2008; Tan et al., 2010).

Ageing-associated changes in immune-regulating properties of astrocytes or T-cells have been proposed to play a role in microglial priming (Dilger and Johnson, 2008). It could also be that age-related priming reflects the cumulative effects of repeated immune activations over the lifetime of an individual. The observation of microglial priming in animal models of neurodegenerative diseases, characterised by chronic or recurrent inflammation, supports this hypothesis (Dilger and Johnson, 2008; van Harten et al., 2012).

Based on the above, it can be hypothesised that the manifestation of POCD depends on the susceptibility of the brain to neuroinflammatory processes and inflammatory priming. General characteristics of brain areas make some regions more vulnerable to inflammatory insults than others. For example, it is known that the hippocampus is especially sensitive to the effects of inflammation (Yirmiya and Goshen, 2011), and memory impairment is more commonly seen after surgery than impairments of executive functions (Price et al., 2008).

Inter-individual differences have been shown for several aspects of the neuroinflammatory pathways. One example is the large inter-individual variation in chemokine receptor expression that has been associated with inflammatory activity and tissue damage in patients with multiple sclerosis (Fox et al., 2008). Similarly, the response of microglia to a pro-inflammatory stimulus, which is hypothesised to be a key factor in POCD development, has been shown to vary between individuals (Meeuwse et al., 2005). In line with age-associated priming, these inter-individual differences may depend on different immune regulatory properties or exposure to recurrent priming stimuli, such as stress, a diet rich in fat and simple carbohydrates, inflammatory history and alcohol use (Bilbo, 2010; Bilbo and Tsang, 2010; Hinwood et al., 2011; Kanoski and Davidson, 2011; McClain et al., 2011; Tynan et al., 2010).

6.2. Pre-existing neurodegeneration

Ageing has been associated with neuron damage and abnormalities in various brain regions (Shankar, 2010). Imaging studies in young and older subjects have revealed that during cognitive tasks, the activation pattern in older subjects is more widely distributed across brain areas, especially in the frontal regions (Baddely et al., 2009; Goh and Park, 2009; Stern, 2009). It has been hypothesised that the increased activation pattern seen with advancing age is a mechanism to compensate for the reduced cognitive efficiency following neuronal damage (Goh and Park, 2009; Stern, 2009).

In pathological conditions such as Alzheimer's disease (MRC CFAS, 2001), a disjunction between brain damage and cognitive impairment has long been noted. This discrepancy is explained by cognitive reserve (Nithianantharajah and Hannan, 2009; Stern, 2002). The theory of cognitive reserve holds that the brain can compensate for brain damage, by using a reserve present within the brain. The reserve depends on the extent of pre-existing neuronal networks, which is determined by the number of neurons and synapses, neuronal plasticity and efficiency (Nithianantharajah and Hannan, 2009; Stern, 2009). Individuals with a greater reserve can sustain more neural damage or neuronal loss before symptoms of cognitive decline present themselves (Bekker et al., 2010). These processes may also play an important role in POCD development. Cognitive reserve can be influenced by environmental and genetic

factors, such as toxins, ischaemia and neurodegenerative diseases that can lead to pre-existing neuronal damage. Many of these detrimental effects are brain-area specific. For example, hypertension has been associated with detrimental changes in the frontal lobe, whereas Alzheimer's disease mainly affects the medial temporal cortex (Buckner, 2004). Another example comes from subjects with type 2 diabetes. In an MRI study, Gold et al. (2007) demonstrated that patients with type 2 diabetes exhibit impairment in hippocampus-dependent memory functions that coincide with the presence of hippocampal atrophy.

In contrast to the above, Bekker et al. (2010) showed that patients with pre-existing memory impairments have a higher risk of developing executive impairments than memory impairments after surgery. This seems to suggest that pre-existing damage in memory function does not make this domain more vulnerable than other cognitive functions for surgery-induced impairments. However, the authors themselves indicate that the results are probably due to floor effects in the cognitive tests used, i.e. the test can only measure a deviation from normal cognition but is not sensitive enough to measure an additional cognitive decline when cognitive dysfunction is already present (Bekker et al., 2010).

In a recent article Murray et al. (2010) demonstrated that mice with pre-existing hippocampal neuron damage were more vulnerable than their healthy counterparts, to hippocampal memory decline, but not to non-hippocampal memory decline, after an inflammatory challenge. This indicates that pre-existing neuron damage may indeed determine the vulnerability to the inflammation-mediated cognitive changes a patient will experience after surgery. Accordingly, it has been shown that patients who are likely to have pre-existing neuron damage, are at higher risk of developing POCD. Patients with metabolic syndrome, mild cognitive impairment and patients who have fully recovered from a stroke for example, have a higher risk of developing POCD (Bekker et al., 2010; Hudetz et al., 2011; Monk et al., 2008; Silverstein et al., 2007).

In summary, the large variability in cognitive dysfunction after surgery can be caused by inter-individual differences in the susceptibility of neural networks to surgery-induced deterioration. This susceptibility may be the result of genetics and environmental stimuli that influence the vulnerability for neuroinflammation or cause pre-existing neurodegeneration. Thus genetic factors and life history determine if and how POCD manifests itself.

7. Future perspectives

Research into cognitive deterioration after surgery can be divided in two distinct fields that seem to have developed in different directions (Fig. 1A). In this review we attempted to bridge the translation gap between these fields, using existing literature concerning POCD, to gain insights into the cognitive decline that characterises POCD and the brain areas involved. The most important outcomes are: (1) POCD encompasses a wide range of cognitive impairments; (2) POCD affects larger areas of the brain; and (3) individual variation in the vulnerability of neuronal networks may determine if and how POCD manifests itself. These findings indicate that to bridge the translational gap between the clinical and pre-clinical research on POCD, the condition should be looked at from another perspective (Fig. 1B). There are two important changes that should be considered. First, the change from a general definition of cognitive decline after surgery to considering the whole spectrum of cognitive functions and domains involved in this condition. Second, the change from only comparing group means, to analysing inter-relationships between cognitive complaints and physical and mental patient characteristics.

Fig. 1. Schematic representation of the current (A) and future (B) perspectives of pre-clinical and clinical POCD research, considering: (1) the research focus; (2) the way of determining POCD; (3) the period after surgery in which cognition is studied; and (4) the parameters that are included in the study of POCD. Font size indicates the relative importance of the factors. (A) The underlying mechanism of POCD has primarily been studied in pre-clinical models, while clinical studies have been used to determine the incidence and risk factors for POCD. This has led to differences in the approach to study POCD. Pre-clinical studies mainly focus on hippocampal dysfunction within one week after surgery, in which behaviour and levels of inflammatory factors in plasma and hippocampal brain tissue serve as parameters. Clinical studies, however, define POCD as a decline of more than one SD or 1.96 Z-score on two or more neuropsychological tests that persists for more than one week after surgery. Few of these studies have included physiological parameters. These differences in research perspectives have led to a translational gap POCD research, which might lead to incomplete or incorrect assumptions about the underlying mechanisms. (B) Pre-clinical and clinical studies should include inter-individual variation in their research focus to gain insight into the factors that predispose certain individuals to develop POCD. In addition, clinical studies should include blood parameters and imaging techniques to make the connexion with pre-clinical physiological outcomes. Furthermore, research on POCD should take the whole spectrum of cognitive changes after surgery into account. To aid translation to the clinical setting, pre-clinical studies should expand the time frame of their experiments to include cognitive changes that persist for more than one week after surgery.

7.1. Pre-clinical research

For the pre-clinical models of POCD to be effective it should be possible to adequately translate the pre-clinical findings to the human situation. Therefore, these models should take into account all cognitive functions that may be affected by surgery into account, rather than focusing on hippocampal functions. In rats and mice, there is a broad range of behavioural tests available that can be used to study cognitive performance in several domains. Pre-clinical models should relate the outcomes of these cognitive tests to changes in the associated brain areas on a cellular and molecular level. Moreover, since POCD constitutes persisting impairments, pre-clinical models should extend their time-frame. It can be questioned whether POCD occurs in a comparable time frame in rodents and humans, since differences in metabolism and recovery can be expected between species. Furthermore, humans usually have a pre-existing ailment or trauma before undergoing surgery, whereas laboratory animals do not. This might further alter the time-frame in which POCD occurs. It may, therefore, not be realistic to expect POCD to persist for the same period of time in laboratory rodents and human patients. To be able to make a distinction between sickness behaviour and delirium symptoms versus persisting cognitive problems after surgery, we suggest POCD research should include measurements of cognitive function for more than one week after surgery.

In accordance with clinical studies, animal models should take into account individual variation in test outcomes. Correlating the test outcomes with factors of interest to the underlying mechanism, will lead to valuable insights. This is especially important when it comes to studying the persisting impairment of POCD, since this is only seen in a small percentage of individuals, and group averages are not likely to differ significantly. Moreover, by studying inter-individual variation in POCD, insight can be gained into factors that predispose individuals to develop POCD or, conversely, protect an individual from developing the condition. Additionally, specific information about the interplay between risk-factors for POCD, individual vulnerability and cognitive outcome can be gained from animal models with a known or induced vulnerability (Murray et al., 2010). Examples are models of neurodegenerative diseases, hypertension, or tissue specific genetically modified strains.

7.2. Clinical research

Clinical studies should not only focus on whether POCD is or not, but also on the separate cognitive test outcomes. A broad spectrum of cognitive tests should be used to determine which cognitive domains are affected, including tests for at least the memory, attention and information-processing domains. By using neuropsychological of which the brain areas involved are known, or by including imaging techniques in the analysis of POCD, additional insight can be gained into the brain regions affected and the possible use of compensatory mechanisms.

In addition to considering the whole spectrum of cognitive impairments, the variation in manifestation of POCD between individuals should also be taken into account. By analysing information about pre-operative cognitive functioning, post-operative test performance, and the brain function of each individual patient, patterns can be detected in the development of POCD. These patterns will provide information about the brain areas related to certain types of cognitive deterioration after surgery. As such, insight into the mechanisms underlying POCD will be gained. The outcomes of such studies will provide a rationale on which to base pre-clinical research models of POCD. Moreover, knowledge of the cognitive domains affected could be used to develop and

optimise test batteries for POCD thereby improving diagnostic methods.

Perhaps even more importantly, by relating individual manifestations of POCD to patient history and characteristics, an assessment can be made of the risk factors for each type of cognitive decline. This knowledge can then be used to develop an individual-based risk analysis for cognitive deterioration after surgery. Interventions can then either consist of tackling the factors that increase POCD risk or targeting the pathophysiological mechanisms.

8. Conclusion

Historically, the classification of a range of cognitive impairments after surgery under the common denominator 'POCD' has enabled researchers to better understand this condition. For diagnostic and policy purposes, this common denominator will still prove very important. However, to truly understand the underlying mechanisms of postoperative cognitive impairment and to develop effective intervention strategies, the whole spectrum of cognitive impairments and individual variation should be taken into account. For this purpose, true translational research is mandatory.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.bbi.2012.06.004>.

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