

A Topical Review on Executive Functioning in Chronic Non-malignant Pain:  
Do Different Neurocognitive Dysfunctions in Chronic Non-malignant Pain Reflect a  
Common Underlying Process?

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### **Abstract**

Clinical observations reveal that cognitive impairments are frequently reported in chronic non-malignant pain patients, and impairments in memory, attentional and executive functions have been found by performance-based neuropsychological tests. To date, no systematic review has been conducted on cognitive impairment in this patient group. There is a need for clarification and systematization of the studies in this field. The aim of this study was to conduct a topical review on executive impairments in chronic pain, and systematize findings based on theoretical frameworks on executive functions and models of pain and attention. A database search identified 30 studies where evidence points towards deficits in executive function in chronic non-malignant pain. It is here concluded, based on the existing evidence, that the impairments might reflect an underlying deficit in executive control. This is supported by both clinical and experimental studies. In addition, executive control deficits are closely correlated with subjective reports of cognitive difficulties. This has implications for treatment of these symptoms. There may be possibilities to target this specific deficit by high-demanding working memory training programs. Future research should use methods from cognitive psychology to test out theory-driven hypotheses about the possibility of an underlying executive control deficit in chronic pain.

Keywords: executive functions, chronic non-malignant pain, executive control, inhibitory control





### **Introduction**

Executive functioning has broadly been defined as the processes that enable us to do complex cognitive tasks, such as planning, organization, control of conflicting thoughts, perform goal-directed behaviors and the initiation and assessment of the consequences of our actions (Elliot, 2003). These are high-level cognitive functions associated with the frontal lobes (Stuss et al., 2002), and are critical for adaptive human behavior in complex environments (Jurado & Rosselli, 2007). It has been proposed that executive functions and self-regulatory deficits are part of etiology and maintenance of chronic pain conditions (Solberg-Nes, Roach & Segerstrom, 2009). Chronic pain is best understood in a biopsychosocial framework, where complex interactions between cognitive, emotional and physiological factors exist, and the ability to self-regulate is important for management of symptoms. This is reflected in the definition of pain as “an unpleasant sensory and emotional experience that is associated with actual or potential tissue damage, or described in terms of such damage” (Merskey & Bogduk, 1994, p. 210). Epidemiological studies estimate that 19 % of the adult population in Europe experience chronic pain of moderate to severe intensity, and 40% of this population does not perceive received treatment as adequate. Chronic pain can thus be defined as a major health care problem in Europe, and more research is needed on etiology and treatment of this patient group (Breivik, Collett, Ventafridda, Cohen & Gallacher, 2006).

### **Subjective reports relate to executive difficulties**

The biopsychosocial complexity of chronic pain is in line with clinical observations that chronic pain patients often report problems with multiple symptoms other than pain. This includes depression, anxiety, fatigue and sleep problems. Studies find that 54 % of chronic pain patients report difficulties with at least one aspect of cognitive functioning (McCracken, & Iverson, 2001), and this is found in 70 % of some patient groups (Katz, Heard, Mills &

Leavitt, 2004). There is some consistency in the aspects of cognitive functioning where difficulties are reported. The most frequent have been forgetfulness (29%), difficulties maintaining attention (18%) and difficulties with concentration and thinking (16,5%, McCracken & Iverson, 2001). These areas of perceived difficulties have been confirmed by several researchers (Glass, 2010; Park, Glass, Minear, & Crofford, 2001). In qualitative studies patients report not being able to operate at the same mental acuity as prior to onset of pain. They report problems with keeping focused, feel more disorganized and have difficulties with planning ahead, which are descriptions of central aspects of executive functions. Patients report this to be problematic specifically when driving and in work settings (Arnold et al., 2008). Patients have ranked cognitive difficulties among the top five symptoms with greatest impact on their everyday functioning (Mease, 2005). Research on cognitive difficulties is however relatively sparse compared to the amount of research on pain and tenderness (Ambrose, Gracely, & Glass, 2012), and cognitive impairment in chronic pain conditions can be considered greatly understudied (Williams, Clauw, & Glass, 2011).

### **Empirical findings of cognitive impairment in chronic pain**

Reviews conclude that there is substantial evidence for cognitive dysfunction in attentional capacity, processing speed and psychomotor speed in patients with chronic pain as measured by performance-based neuropsychological tests (Hart, Martelli, & Zasler, 2000). Findings are consistent when studying groups of mixed non-malignant pain conditions (Sjögren, Christrup, Petersen, & Højsted, 2005), as well as specific diagnoses (Glass, 2010; Park et al., 2001; Weiner, Rudy, Morrow, Slaboda & Lieber, 2006), and chronic pain conditions with different etiologies (Apkarian et al., 2004a; Povedano, Gascón, Gálvez, Ruiz, & Rejas, 2007). Impairments have been found in diverse memory functions such as long-term spatial memory (Luerding, Weigand, Bogdahn, & Schmidt-Wilcke, 2008), and most robustly in working memory functions (Antepohl, Kiviloog, Andersson, & Gerdle, 2003;

Dick & Rashiq, 2007; Grace, Nielson, Hopkins, & Berg, 1999; Luerding et al., 2008; Oosterman, Derksen, van Wijck, Veldhuijzen, & Kessels, 2011; Park et al., 2001; Weiner et al., 2006). Impairments are found in psychomotor speed (Lee et al., 2010; Sjøgren et al., 2005; Veldhuijzen, Sondaal, & Oosterman, 2012) and on measures of general cognition (Oosterman et al., 2011; Weiner et al., 2006). Impairments are also found in attentional functions (Dick, Eccleston & Crombez, 2002; Dick & Rashiq, 2007; Eccleston, 1994; Grace et al., 1999; Grisart & Plakhi, 1999; Oosterman et al., 2011; Veldhuijzen, Kenemans, de Bruin, Olivier, & Volkerts, 2006), and in executive functions (Oosterman, Derksen, Van Wijck, Kessels, & Veldhuijzen, 2012), specifically in tasks measuring interference (Leavitt & Katz, 2006). It has been suggested that complex tasks of attention may tap executive functions (Moriarty, McGuire, & Finn, 2011).

### **Methodological shortcomings in the literature**

Many researchers have found the self-report of cognitive difficulties in chronic pain to be overestimated compared to actual performance (Grace et al., 1999; Suhr, 2003), while others have found the complaints to have some accuracy (Dick, Verrier, Harker & Rashiq, 2008; Glass, Park, Minear & Crofford, 2005; Park et al., 2001; Verdejo-Garcia, Torrecillas, Calandre, Delgado-Rodriguez, & Bechara, 2009). The cognitive impairment found is often attributed to factors other than pain itself, such as depression (Suhr, 2003), and some even point to the intentional or unintentional exaggeration of symptoms in some chronic pain populations (Etherton, Bianchini, Ciota, Heinly & Greve, 2006; Greve, Ord, Bianchini & Curtis, 2009; Meyers & Diep, 2000). Several researchers have addressed methodological shortcomings in the literature. Even though many studies use well-validated tests when examining cognitive functions, large variations exist in experimental conditions and which confounding variables are controlled for (Hart et al., 2000). Studies often use chronic pain groups with mixed etiologies (Moriarty et al., 2011), and inadequate recruitment strategies

(Berryman et al., 2013). These methodological shortcomings clearly need to be addressed, yet since the first review published about a decade ago (Hart et al., 2000), only one review that examine cognitive function in chronic non-malignant pain has been published (Moriarty et al., 2011). That particular review presented a more refined but yet unsystematic review including both clinical and pre-clinical studies, focusing on possible mechanisms causing impairment. In addition, a systematic review and meta-analysis have also been published that focus specifically on working memory functioning in chronic pain (Berryman et al., 2013). This is however limited to this one aspect of cognitive function. Therefore, to this author's knowledge, no systematic evaluation that adequately captures cognitive impairment in non-malignant chronic pain has been published.

### **Conceptual considerations on executive functions**

Attentional and executive functions share many features, and it is difficult to separate them on a conceptual level (Oosterman et al., 2012). Attention involves multiple functions such as sustained, divided and selective attention, and these overlap with what is defined as executive functions (Moore, Keogh & Eccleston, 2009). The definition of executive functions is an area of great debate. Many attempts to define executive functions result in the naming of various abilities, and this reflect how executive functions are not seen as a unitary concept (Elliott, 2003). This debate of unity and diversity of executive functions first addressed by Teuber (1972) has been a central theme of debate in neuropsychological literature (Duncan, Johnson, Swales, Freer, 1997; Jurado & Rosselli, 2007).

Naturally following the problem of definition is the issue of measurement of executive functions. Executive tests show test-retest reliability and uncertain validity (Rabbitt, 1997), which have made it difficult to make distinctions between “executive” and “non-executive” tasks. One central issue is the task impurity problem (Burgess, 1997). Since the nature of executive functions is to operate on other cognitive processes, naturally the measures of

executive functions include systematic variance that is attributable to other processes associated with the specific context of the task. An example is the Stroop-task, where the interesting feature related to executive functions is the interference score, yet the outcome might be confounded by others factors such as color processing and articulation speed (Miyake & Friedman, 2012). This explains why a low score on an executive task do not necessarily mean deficits in executive function (Miyake & Shah, 1999).

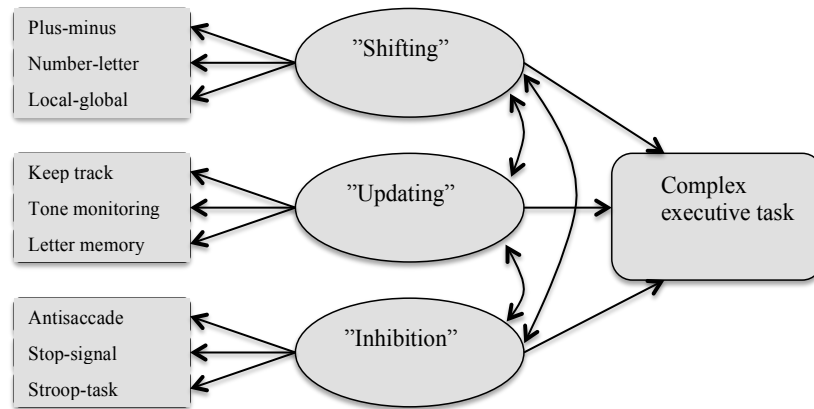
These conceptual considerations are also evident in related conceptual functions such as working memory, which is a term used interchangeably with executive functions. In the recent published systematic review and meta-analysis on working memory function in patients with chronic pain, a definition of working memory as a non-unitary construct was used (Baddeley, 2007), and all studies using the terms “short-term memory”, “executive function”, “working memory” and “running memory” were included. Within these studies, twenty-one different working memory tests were used, encompassing nine different working memory constructs. Still, a moderate effect of cognitive impairment in working memory in chronic pain was found compared to healthy controls (Berryman et al., 2013). It can be interpreted that despite of the different constructs, definitions and operationalization used, they all capture a common phenomenon.

### **An empirical model of executive functions**

As a possible solution to conceptual difficulties, Miyake, Friedman, Emerson, Witzki & Howerter (2000) have developed a model of executive functions based on latent variable analysis. In this particular analysis, nine different tasks were chosen that share little variance attributable to non-executive cognitive processes. Then, what is common in the tasks was statistically extracted, and used as a more “pure” measure of executive functions. The model postulates that executive functions consist of three separate but yet interdependent functions; mental set shift or mental flexibility, updating and monitoring working memory, and the

inhibition of pre-potent responses. Structural equation modeling confirms that these three functions contribute individually to performance on complex executive tasks, such as Wisconsin Card Sorting task and Tower of Hanoi (Miyake et al., 2000). Updating and monitoring of working memory involves a dynamic process of monitoring and coding incoming information for relevance to the task at hand, and then appropriately revising items held in working memory by replacing old and no longer relevant information with new relevant information (Van der Linden, Bredart, & Beerten, 1994). The shifting ability has traditionally been defined as the ability to shift between tasks and mental sets, and involve a disengagement of an irrelevant task set and the subsequent active engagement of a relevant task set (Rogers & Monsell, 1995). A newer and more appropriate definition involves the ability to perform a new operation in the face of proactive interference or negative priming. An important term here is the ability to inhibit “proactive interference”, which have been discussed by Engle (2002). Cognitive inhibition as an executive function can be defined as the ability to inhibit dominant, automatic, prepotent responses, and can be considered a deliberate and controlled process (Roberts, Hager, & Heron, 1994).

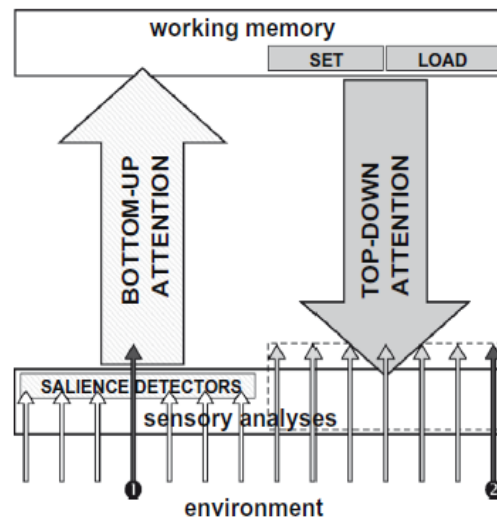
Confirmatory factor analysis indicates that these executive functions are moderately correlated with each other, and thus share some underlying commonality. The question of the nature of the commonality has also been explored, where updating and monitoring working memory and inhibition of prepotent responses have been proposed as possible candidates (Miyake et al., 2000).



*Figure 1.* The empirical model of executive functions by Miyake and colleagues (2000) includes three commonly used tasks thought to measure each of the executive functions. It shows how the three functions are correlated yet separable, and together makes the possibility for the execution of complex mental tasks.

## A neurocognitive model of pain and attention

Research on the relationship between pain and cognitive function should be guided by theoretical frameworks. Traditionally the literature on attention and pain has been guided by theories of limited resource capacities in human cognition. An extended version of the limited resource theory has been proposed that integrates several hypotheses about pain and its effects on cognition. The model makes a distinction between top-down and bottom-up attention modes. The interesting feature about this model is that bottom-up attention to pain can be modulated by top-down variables, either by directing attention away from nociceptive stimuli, or by facilitating attentional capture. Further it is hypothesized that top-down modulation acts through attentional load and set features. Attentional load refers to the amount of attention that is invested in a task, and attentional set is the mental set of stimulus features that participants use to identify task-relevant stimuli (Legrain et al., 2009).



*Figure 2.* The neurocognitive model by Legrain et al. (2009) show the interactive nature of pain and attention. Pain can capture attention through bottom-up and top-down attention pathways. Top-down monitoring are directed by cognitive goals activated in working memory, and these goals can either define the features of the stimuli that are relevant (attentional set) or the amount of attention needed to achieve the goal (attentional load). Top-down selection increases responses to goal-relevant signals (grey arrows) and inhibits responses to goal-irrelevant signals.

## Executive control

When examining attentional and executive functions in chronic non-malignant pain populations, it should be considered whether deficits reflect a specific underlying deficit or a decline in a more basic cognitive ability. When having neuropsychological models of executive functions in mind, inhibition of prepotent responses stands out as a candidate (Miyake et al., 2000). Different terms for this executive control concept have been proposed in the literature. Among these are controlled attention (Engle, 2002; Engle, Tuholski, Laughlin, & Conway, 1999), cognitive control (Depue, Banich, & Curran, 2006; Jacoby, Shimizu, Daniels, & Rhodes, 2005), executive attention (McCabe, Roedinger, McDaniel, Balota, & Hambrick, 2010), inhibitory control (Hasher, Lustig, & Zacks, 2007), attentional control (Balota, Law, & Zevin, 2000) and executive control (Logan, 2003). All of the terms



are included in this topical review, but executive control is here chosen as the main term both covering the executive and the inhibition aspect.

According to the neurocognitive model, when evaluating pain and its effect on attention, one can hypothesize that patients may have difficulties with executive control over nociceptive interference, which may correspond to the top-down modulation and attentional load hypothesis. Another possibility is the combination of top-down and attentional set hypothesis, where patients have excessive expectations or attention to bodily signals in their attentional set (Legrain et al., 2009).

### **The aims of this study**

After several decades of research on cognitive impairment in chronic non-malignant pain, there should no longer be doubt that these patients experience cognitive difficulties to a moderate degree, which cannot be explained by other factors such as depression, anxiety or sleep problems. As seen in earlier reviews (Hart et al., 2000; Moriarty et al., 2011), research in this area is characterized by a myriad of studies on various non-malignant chronic pain conditions. These studies are often explorative and without theory-driven hypotheses, and single tests are often used to measure specific functions. There has been a lack of reviews that tie specific findings to theoretical concepts of pain and its effects on cognitive function. It has in this authors view limited the conclusions to be drawn about the extent to which executive functions are the central area of impairment. It has further limited the debate on mechanisms or underlying processes that may be impaired in chronic non-malignant pain. In a sense, one is still on the surface of what the outcome of cognitive impairment in chronic pain might be, and lack knowledge of possibilities for cognitive underpinnings or processes that might be serving as a common underlying factor that is impaired in chronic pain.

The aim of this study is to conduct a topical review of executive functioning in chronic non-malignant pain, to extract what can be concluded about impairments in executive

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functions in this patient group. This topical review will further explore the central question if a common underlying process can explain cognitive impairment found in chronic non-malignant pain. The main research questions are:

- 1) Do cognitive impairments in chronic non-malignant pain relate to deficits in executive control functions?
- 2) Can executive control dysfunctions be explained by a common underlying process?

### **Methods**

#### **Search strategy**

Relevant records were identified through a database search conducted in PubMed (n=876). “Executive control”, “attention control”, “working memory”, “mental flexibility”, “controlled attention” and “inhibitory control” were used as search words in addition to “chronic pain”. These search words were selected on the basis of best describing the most common executive functions, as reflected in the functions included in an empirical model of executive functions (Miyake et al., 2000). Further, the search words reflect commonly used terms of the executive control concept (Balota et al., 1999; Depue et al. 2006; Engle, 2002; Hasher et al. 2007; Jacoby et al., 2005; McCabe, 2010). In addition, when consulting with experts in the field, more studies were included on the basis of their recommendations (n=9). Reviews were read and searched for additional original references.

#### **Study selection**

To be included in this review, the studies had to compare aspects of executive functions in chronic non-malignant pain compared to healthy controls or to norms of the

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normal population. Studies assessed for eligibility were excluded if they were animal studies (n=9), if they did not study a chronic non-malignant pain condition (n=17), or if the chronic non-malignant pain group had no control group or norm comparisons (n=7). Studies were also excluded if they were experimental studies with induced pain, also if it were induced in clinical populations (n=15). They were excluded if the cognitive function of study were not related to executive functions (n=18). Studies were also excluded if they compared cognitive function according to attentional or emotional bias (n=33). Reviews and meta-analysis were also excluded (n=11). All abstracts in the search was read and evaluated according to the inclusion criteria.

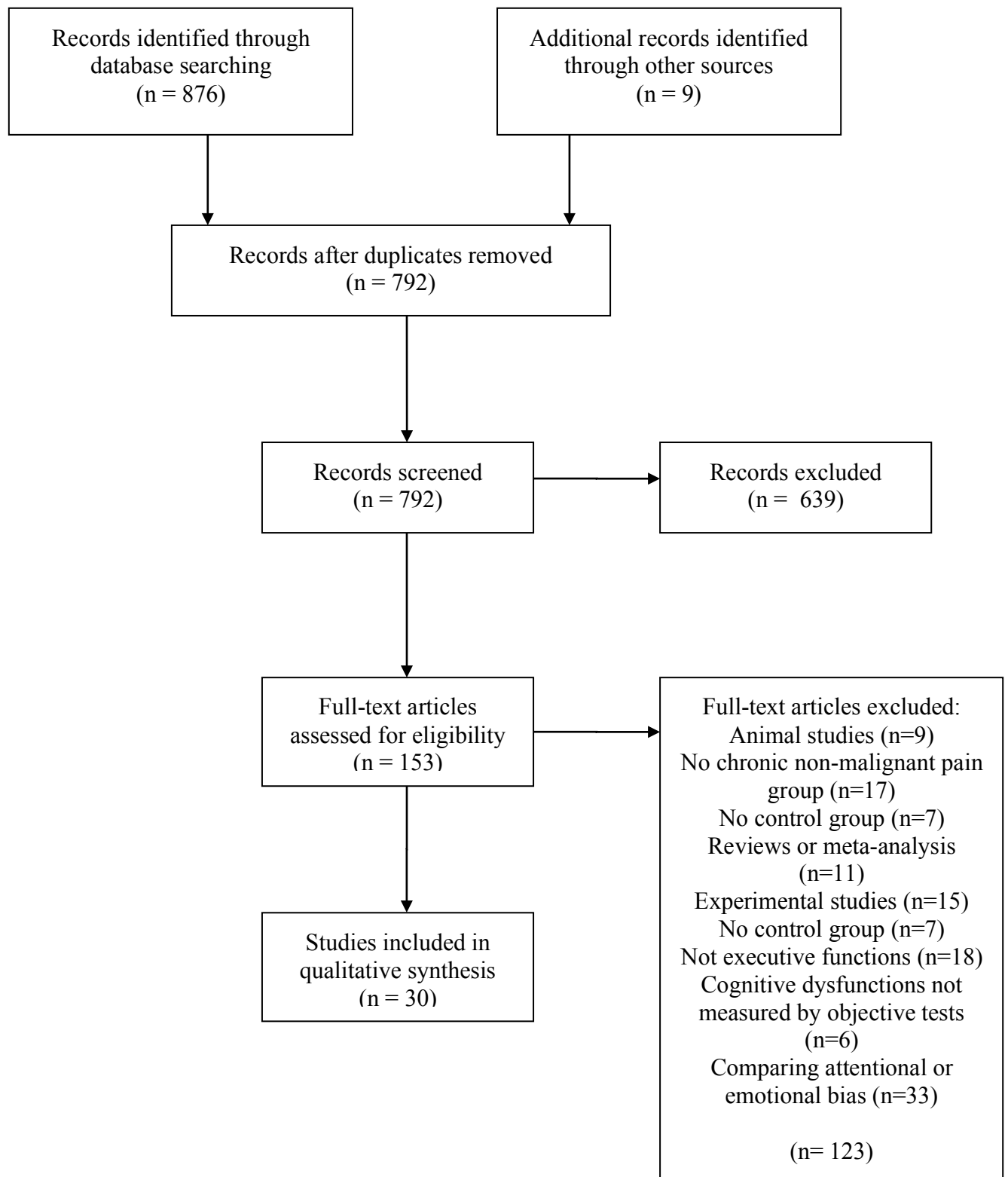
### **Inclusion criteria**

Studies were included if they described some aspect of executive functions in chronic non-malignant pain. The studies had to measure executive functions using well-validated neuropsychological tests.

### **Exclusion criteria**

Studies were excluded if the population studied had neurological disorders, or had suffered traumatic brain injury. Studies were also excluded if the population of study was below the age of 18, or if studies compared attentional bias to emotional stimuli. Papers not written in English were excluded.

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*Figure 3.* The flowchart according to Moher, Liberati, Tetzlaff & Altman (2009), show the search process. The database search identified 876 records. Together with the nine records found through other sources, 792 remained when duplicates were removed. These were screened according to the main criteria, and 153 full-text articles were further assessed for eligibility. 123 of these were excluded for various reasons (see Figure 3), and 30 studies were included in the qualitative synthesis.

## Results

Table 1

*The table shows the 30 studies included in the topical review, systematized according to the cognitive functions studied.*

Type of chronic pain	Cognitive functions tested	Neuropsychological tests used	Findings related to pain and its effect on cognitive functions	Other parameters considered	Reference
Chronic pain patients (n=25), non-patient group (n=25)	Immediate and delayed recall	Test of immediate and delayed recall (word lists)	No significant group differences between patient group and non-patient group on memory test of immediate recall. Chronic pain patients recalled significantly more pain-related words than the control group.	No additional control variables were included	Pearce et al. (1990)
Chronic low back pain (n=24), rheumatoid arthritis (n=33)	Immediate recall	Wechsler Memory Scale III (WMS-III)	Patients with rheumatoid arthritis and low back pain performed significantly worse on all measures compared to norm data. No significant differences found between groups.	Depression and anxiety (HADS), Fear avoidance belief questionnaire	Jorge et al. (2009)
Fibromyalgia (n=28), mixed chronic pain (n=27), and healthy controls (n=21)	Attention, Verbal and non-verbal WM	WCST, SCWT, Subtests from WAIS-III: arithmetic, digit span, letter-number sequencing, digit symbol, symbol search, TMT, PASAT, Controlled Oral Word Association	No significant group differences on any of the neuropsychological tests, after controlling for pain severity, depression and fatigue. No group differences in the total number of impaired scores.	Depression (BDI), Fatigue severity scale	Suhr (2003)
Fibromyalgia (n=30), matched healthy controls (n=30)	Attention, WM	TEA, ACT, Reading span test	Significant group differences found, also when controlled for depression, anxiety, sleep disruption. No group differences when controlling for pain intensity.	Health-related quality of life (15D), anxiety and depression (HADS), sleep dysfunction	Dick et al. (2008)
Chronic pain (n=24)	Attention, WM	TEA, reading span test, Spatial span test	Two-thirds of participants with chronic pain had scores in the clinically impaired range on attentional tasks.	Catastrophizing (PCS), depression and anxiety (HADS), sleep quality	Dick & Rashiq (2007)

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Mixed group of chronic non-malignant pain (n=72)	Attention, WM	PASAT, Letter-number sequencing from WAIS-III, California Verbal Learning Test-II, SCWT	About 20% of the patients performed below cut-off for clinically significant impairment compared to population norms.	Depression (BDI)	Landrø et al. (2013)
Fibromyalgia (n=30), matched healthy controls (n=30)	Attention, WM	WMS-III-R, Rey Auditory Verbal learning test, PASAT, Symbol digit modalities test	The fibromyalgia group performed in the normal range, but scored significantly poorer on immediate and delayed recall, and sustained auditory concentration than matched group.	Sleep quality (PSQI), Depression (CES-D), the State-Trait Anxiety Inventory	Grace et al. (1999)
Patients with musculoskeletal pain in the lumbosacral area (n=64), and healthy controls (n=20)	Attention, WM	The sequential number-letter combination test, DSST, forward and backward number series repetition test	Patients complaining of memory impairments performed significantly less well on the 12-word test with delayed reproduction, and patients complaining of impaired attention performed the digit symbol substitution test significantly worse than patients lacking these complaints.	Catastrophizing (PCS), anxiety (Spielberger–Hanin self-assessment anxiety Scale), Depression (Hamilton Scale), psychological distress (SCL-90)	Melkumova et al. (2011)
Mixed chronic pain (n=14), healthy controls (n=30)	Attention, WM	Attentional capacity probe task (in addition to ERP)	Chronic pain group showed a different speed-accuracy trade-off. Chronic pain patients showed faster reaction time responses and higher error rates compared to controls.	Depression (CES-D), Anxiety (Spielberger State-Trait Anxiety scales), the Profile of Mood State	Veldhuijzen et al. (2006b)
Chronic widespread pain (n=266), no-pain group (n=1273)	WM, Psychomotor speed	Rey-Osterrieth complex figure test, the Camden topographical recognition memory, DSST	Chronic widespread pain was associated with slower psychomotor processing speed, no significant findings on the other tests.	Depression (BDI-II), Reuben's Physical Performance test (PPT)	Lee et al. (2010)
Chronic non-malignant pain (n=91), healthy matched controls (n=64)	Non-verbal WM	Continuous Reaction time (CRT), Finger Tapping Test (FTT), PASAT, MMSE	Significant impaired function in the whole chronic pain sample was found on CRT and FTT, reflecting sustained attention and psychomotor speed.	Did not include any psychological variables	Sjögren et al. (2005)
Fibromyalgia patients (n=20)	Verbal WM, non-verbal WM	CVLT, Rey Visual Design Learning Test (RVDLT), digit span backward, Corsi block span, TMT	Fibromyalgia patients had significantly reduced working memory and impaired non-verbal long-term memory compared to norm data.	Depression (BDI)	Luerding et al. (2008)
Fibromyalgia patients (n=25), patients with major depression	WM	Digit Span Forward task, Randt memory test, Code memory test, Word fluency task, Kimura	Both fibromyalgia group and depressed group showed significant impairment in long-term memory tasks requiring effortful processing	Depression (BDI)	Landrø et al. (1997)

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(n=22), healthy controls (n=18)		recurring recognition figures test, Incidental memory task, Similarities test	compared to healthy controls. When controlling for depression, only fibromyalgia patients with a history of MDD showed significant impairment.		
Fibromyalgia (n=19), healthy controls (n=22)	WM	N-back memory task (during fMRI)	The fibromyalgia group performed significantly worse on accuracy and response time compared to healthy controls.	Depression (BDI) and anxiety (BAI)	Seo et al. (2012)
Fibromyalgia (n=23), age-matched healthy controls (n=23), 20 year older adults (n=23)	WM	Reading span, computational span	Fibromyalgia patients performed significantly worse on all measures, except for processing speed.	Depression (BDI and GDS), anxiety, fatigue	Park et al. (2001)
Fibromyalgia (n=15), Rheumatoid arthritis (n=15), healthy controls (n=15)	Verbal WM immediate visual memory	Stroop test, the digit test, number key test (WAIS-III), Rey Complex Figure test (ROFCT), spatial recall test, visual reproduction test, WMS-III, BVFRT, BJLT, Road Map Test	Fibromyalgia and rheumatoid arthritis groups performed significantly poorer on tests of short-term memory, spatial orientation, and figure perception compared to healthy controls. Rheumatoid arthritis patients performed poorer on visuoperceptive practices and the speed in visuomotor processing, and fibromyalgia in long-term visual memory deficits.	Duration of pain illness 0-5 years (control effect of chronicity)	Roldan-Tapia et al. (2007)
Whiplash-associated disorder (n=30), healthy controls (n=30)	Verbal WM, non-verbal WM	Word identification task, mental rotation task, reading span test, matrix test	Patients with whiplash-associated disorders showed poorer performance on tasks measuring working memory.	Did not control for any possible confounding variables	Antepohl et al. (2003)
Chronic pain (n=34), Healthy controls (n=32)	Episodic memory, semantic memory, WM	The Doors test, The Digit Span Backward test, The Category Fluency test, the Story Recall subtest of the Rivermead Behavioural Memory Test, Bourdon- Vos test	Chronic pain group performed worse on tests of working memory and verbal episodic memory compared to healthy controls.	Depression (GDS)	Oosterman et al. (2011)
Chronic low back pain (n=37 using opioids, n=33, without opioids), healthy controls (n=25)	WM, mental flexibility	WAIS-III, TMT, Cambridge automated neuropsychological test battery (CANTAB) subtests; Choice reaction time, pattern recognition memory, spatial span.	Group differences were found in information processing speed between patient groups and healthy controls. Patients receiving opioids had reduced spatial memory capacity, flexibility for concept change and impairments in WM	Depression and anxiety (HADS)	Schiltenswolf et al. (2014)

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			compared to patients not receiving opioids and healthy controls.		
Chronic back pain (n=26), Chronic complex regional pain syndrome (n=12), healthy controls (n=26)	WM, Executive functions	IGT, WCST, Digit span from WMS-III, SCWT	Significant difference was found between groups on IGT suggesting a specific cognitive deficit in emotional decision-making.	Depression (BDI) and anxiety (BAI)	Apkarian et al. (2004a)
Chronic pain (n=34), healthy controls (n=32)	WM, Executive functions	SCWT, TMT, Bourdon-Vos test, Zoo map test	Chronic pain group used longer time completing tests of sustained attention and mental flexibility, did not perform poorer on inhibition or planning tasks.	Depression (GDS), Pain catastrophizing (PCS)	Oosterman et al. (2012)
Fibromyalgia patients (n=18), healthy controls (n=14)	Executive functions, Inhibition	Go/no-go task	No group differences found in either reaction time or accuracy.	Depression (CES-D), anxiety (State-Trait Personality Inventory)	Glass et al. (2011)
Fibromyalgia patients (n=15), healthy controls (n=15)	Executive functions	SCWT, WAIS subscales, IGT, conditional associative learning task (CALT)	Significant group differences found on IGT and CALT, with more perseveration errors in CALT, and disadvantageous decisions in IGT. No differences in Stroop test.	Depression (BDI), and anxiety (State-Trait Anxiety Inventory)	Walteros et al. (2011)
Chronic non-malignant pain (n=56), older adults (mean age: 76,1)	Executive functions, mental flexibility	MMSE, Number-Letter-Switching, Motor Speed subtests of the Delis-Kaplan Executive function System, TMT, DSST	Pain severity was associated with decreased performance on a test of number-letter switching	Depression (Hamilton Rating Scale), sleep quality (PSQI)	Karp et al. (2006)
Chronic low back pain (n=323, older adults), healthy controls (n=160)	Attention, memory, mental flexibility	Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) TMT, Grooved pegboard test	Significant differences found on several measures. Cognitive function was correlated with pain intensity.	Depression (GDS)	Weiner et al. (2006)
Fibromyalgia (n=35), healthy controls (n=35)	Verbal WM, non-verbal WM, attention	The Logical Memory and Paired Associates subtests of WMS-III, The Letter-Number-Sequencing, ACT, Digit span, PASAT,	31,4% of the fibromyalgia group showed impairment on at least one measure of memory encoded free of stimulus competition, 85.7% showed impairment on at least one measure encoded with a source of stimulus competition.	Depression (BDI)	Leavitt & Katz (2006)



## EXECUTIVE FUNCTION IN CHRONIC NON-MALIGNANT PAIN

Fibromyalgia (n=36), healthy controls (n=36)	Executive functions	WCST and IGT (two versions, original and variant version)	Fibromyalgia group showed poorer performance in abstraction and distractibility, showed on WCST on number of categories and non- perseverative errors, no differences in perseverative errors. FM had altered learning curve in IGT, pointing towards impaired emotional decision-making.	Temperament and character inventory-revised (TCI-R)	Verdejo- Garcia et al. (2009)
Fibromyalgia (n=33), healthy controls (n=28)	Attention, executive functions	Attentional network test- interactions task	Fibromyalgia patients showed greater interference, slower reaction times and higher reduction in errors after a warning cue as compared to HC, Interpreted as impaired executive control, reduced vigilance and greater alertness. Sleep dysfunction was a significant predictor for alertness.	Depression and anxiety (HADS), Sleep disturbance (PSQI)	Miró et al. (2011)
Chronic pancreatitis (n=16), matched healthy controls (n=16)	Verbal WM, executive functions, memory	Integneuro test battery, consisting of 13 tests of psychomotor performance, memory, and executive functions	Cognitive impairments found in psychomotor speed and executive functions. Pain duration was the strongest predictor of impairment.	Depression Anxiety Stress Scales (DASS-21), sleep disturbance, opioid use, earlier alcohol use	Jongsma et al. (2011)
Fibromyalgia (n=35), age-matched healthy controls (n=35)	Inhibition, executive functions	SCWT, Multisource Interferences test (MSIT)	Participants did not show evidence of reduced cognitive inhibition capacity, but significantly decreased processing speed.	Depression and anxiety (Brief symptom inventory), pain catastrophizing (PCS)	Veldhuijzen et al. (2012)

*Abbreviations: BDI (Beck Depression Inventory); BAI (Beck Anxiety Inventory); GDS (Geriatric Depression Scale); HADS (Hospital Anxiety and Depression Scale); CES-D (Center for Epidemiologic Studies Depression Scale); PCS (Pain Catastrophizing Scale); PSQI (The Pittsburgh Sleep Quality Index); MMSE (Mini Mental State Examination); PASAT (Paced Auditory Serial Addition Task); WCST (Wisconsin Card Sorting Test); SCWT (Stroop Color Word Interference Test); TEA (Test of Everyday Attention); IGT (Iowa Gambling Task); TMT (Trail Making Test); DSST (Digit Symbol Substitution Test); ACT (Auditory Consonant Trigram)*

### **Discussion**

This topical review has gathered the existing body of research on executive impairment in chronic non-malignant pain. It is to this author's knowledge the first topical review to examine executive functioning in this patient group. Based on neuropsychological theories on executive functions, this topical review includes studies that measure multiple cognitive functions such as attention, memory and learning, and it aims to show how these together complete a picture of deficits in executive functions in chronic non-malignant pain.

#### **Standard executive function tests**

Wisconsin Card Sorting Test (WCST) is considered the most well known test of executive functions, and has been commonly used in chronic pain populations (Apkarian et al., 2004a; Suhr, 2003). Few have however found impairments (Verdejo-Garcia et al., 2009), which seemingly suggest that executive functions in not the area of impairment. The Trail making test (TMT) is often used as a measure of planning or mental flexibility. It is therefore added in this review, even though planning is considered a more complex cognitive function that is difficult to operationalize (Miyake et al., 2000). Some have not found any significant results of impairment on TMT performance in chronic pain compared to norm data (Luerding et al., 2008), or compared to healthy controls when controlling for confounders (Suhr, 2003). Others have only found impairment in the ratio of difference between the two conditions (Schiltenswolf et al., 2014), and yet others impairment in general (Oosterman et al., 2012), or specifically in older adults (Karp et al., 2006; Weiner et al., 2006). As previously mentioned, the most common executive tests correlate differently to specific executive functions (Miyake et al., 2000), and one need to use tests that cover all areas of executive functions, and further examine specific functions to get an adequate picture of executive impairments in chronic non-malignant pain.

### **Working memory**

The deficit found in working memory in chronic pain is considered robust (Berryman et al., 2013; Glass, 2009). Verbal working memory is the function most studied (Antepohl et al., 2003; Dick et al., 2008; Grace et al., 1999; Jongsma et al., 2011; Jorge et al., 2009; Landrø et al., 1997; Luerding et al., 2008; Melkumova, Podchufarova & Yakhno, 2011; Park et al., 2001; Roldán-Tapia, Cánovas-López, Cimadevilla, & Valverde, 2007; Suhr, 2003; Walteros et al., 2011), followed by non-verbal and spatial working memory (Grace et al., 1999; Luerding et al., 2008; Sjøgren et al., 2005; Suhr, 2003). Studies measuring working memory have frequently used various span tasks. In the studies included in this review, multiple versions are used including the reading span (Dick et al., 2008; Dick & Rashiq, 2007; Park et al., 2001), digit span (Apkarian et al., 2004a; Landrø et al., 1997; Leavitt & Katz, 2006; Suhr, 2003), digit span backward (Luerding et al., 2008; Oosterman et al., 2011), computational span (Park et al., 2001), and spatial span (Dick & Rashiq, 2007).

The Paced Auditory Serial Addition Task (PASAT) is a frequently used test of working memory. Findings in chronic pain are mixed. Some are negative when controlling for depression and fatigue (Suhr, 2003), while others indicate that impairment in performance on PASAT is associated with opioid treatment (Sjøgren et al., 2005). Some have found that patients are impaired in PASAT (51,4 % was impaired in the 2 second interval rate), and attributed this to the inclusion of stimuli competition, as the same sample did not show any impairment in tasks not including this element. PASAT has however been criticized for being an anxiety-provoking test (Grace et al., 1999; Reneman, Versteegen & Huitema, 2013), and outcomes may not purely reflect working memory function. On the other hand, dysfunction on the PASAT is in line with other findings that chronic pain patients have good basic attentional skills, but show deficit only in highly demanding tasks (Grace et al., 1999).

### **Executive attentional functions**

Attention is extensively studied (Dick et al., 2008; Grace et al., 1999; Lee et al., 2010; Jorge et al., 2009; Melkumova et al., 2011; Suhr, 2003;). Attention is considered to include several functions such as sustained, divided and selective attention (Moore et al., 2009). There is an overlap between attention and executive control, and tests measuring attention also measures the executive control of attention. Some version of the Stroop-task is often used for this purpose. These studies show mixed results, some find impairments (Landrø et al., 2013) while others do not (Apkarian et al., 2004a; Oosterman et al., 2012; Roldán-Tapia et al., 2007; Walteros et al., 2011). Some have found that initially significant differences in cognitive function as measured by the Stroop-test no longer exist when controlling for pain intensity, depression and fatigue (Suhr, 2003). On the other hand, some researchers have found that 20% of chronic pain patients score below cut-off when using the Stroop test, and that this impairment is significant when parcelling out depressive symptoms (Landrø et al., 2013). Others have found no group differences on the Stroop task when comparing low back pain, complex regional pain syndrome (CRPS) and healthy controls, but instead found significant differences on the Iowa Gambling task, indicating a specific impairment in emotional decision-making (Apkarian et al., 2004a).

### **Studies combining brain imaging and tests of neuropsychological function**

A new line of studies that combine neuropsychological tests with brain imaging give new and intriguing insight. Examples are studies including the n-back task during fMRI (Seo et al., 2012), an attentional capacity probe task in addition to event-related potentials (ERP) measurements (Veldhuijzen et al., 2006b), an emotional Stroop-task in addition to ERP-measurements (Mercado et al., 2013), and a go/no-go task of behavioral inhibition during fMRI (Glass et al., 2011). Although chronic pain patients show deficits at a behavioral level, this is not evident in physiological data during working memory tasks (Berryman et al.,

2013). Interestingly, Glass et al. (2011) did not reveal any differences at a behavioural level, but participants showed altered cortical activation during tasks. It should be mentioned that this study purposely chose a non-demanding task that likely would not show differences (Glass et al., 2011). This new line of research gives more possibilities to gather information about the nature of underlying processes in cognitive impairment in chronic non-malignant pain. To accomplish this, studies need to a larger degree include methods from cognitive psychology (as done by Glass and colleagues, 2011), especially when it comes to study design (Glass, 2009).

### **The complexity of chronic pain and confounding variables**

The nature of the variables that might influence subjective cognitive complaints and cognitive dysfunction in chronic non-malignant pain patients has been heavily discussed. Potential factors include both sensory-discriminative characteristics of pain such as pain intensity, location and duration, as well as more affective-motivational and cognitive-evaluative dimensions (Melzack & Casey, 1968). Reviews on the impact of emotional and pain-related stress conclude that such negative distress play a significant role in cognitive dysfunction independent of pain intensity (Hart, Wade, & Martelli, 2003). Chronic pain conditions are frequently comorbid with many different psychiatric disorders, and these factors can potentially affect cognitive function. The role of such factors have been heavily debated in the literature, and studies have been criticized for not including factors other than depression (Landrø et al., 2013), and as such not seeing the biopsychosocial nature of chronic pain (Reneman et al., 2013). There are no end to the possibility of factors that may influence cognitive function, and further no accepted framework for which factors should be included when conducting research. Some variables have been extensively explored, such as depression (Landrø et al., 1997) and anxiety (Grace et al., 1999). A considerable amount of research has also been conducted on fatigue and sleep problems (Cote & Moldofsky, 1997),

pain catastrophizing (Gracely et al., 2004), and hypervigilance or body awareness (Eccleston, Crombez, Aldrich, & Stannard, 1997). The number and complexity of the factors that may influence cognitive function in chronic pain is central in the methodological shortcomings in studies, and may serve as an explanation for the lack of research in this field (McGuire, 2013).

### **The important role of depression in chronic pain**

Depression has an effect on cognitive function similar to moderately severe brain injury (Veiel, 1997), and has been proposed as a variable potentially confounding results of cognitive impairment in chronic pain. It has been a tendency that cognitive impairment found in chronic pain is no longer significant when depression is controlled for (Landrø et al., 1997; Suhr, 2003). On the other hand, the list is long with studies that find no effect of emotional distress such as symptoms of depression and anxiety on cognitive function (Park et al., 2001; Verdejo-Garcia et al., 2009). It has been stated that whether a significant relationship is found between depressive symptoms and cognitive function is dependent on sampling strategies (Glass, 2009). As an example, Park and colleagues (2001) screened their participants for depressive symptoms and the mean symptom scores of the included participants were below that of mild depression. In Reyes del Paso, Pulgar, Duschek, & Garrido (2012) however, no additive negative effect of depression and anxiety on performance were found even though the sample showed high rates of these symptoms. As Reyes del Paso and colleagues (2011) themselves point out, their study only included a mental arithmetic task assessing mental speed and attention control, and the results cannot be generalized to other areas of cognitive functioning. Another interesting study showed that patients with fibromyalgia was impaired in long-term memory compared to depressive patients and healthy controls, but this effect was not significant when controlling for lifetime history of depression in these patients, indicating that depression was the mediator of the dysfunction (Landrø et al., 1997).

### **Anxiety, sleep problems and fatigue**

Other factors such as anxiety, sleep problems and fatigue may play a considerable role. Early studies found a correlation between anxiety and performance on memory tests (Grace et al., 1999). The general trend has been that when including general anxiety as a mood state, no association between anxiety and cognitive dysfunction has been found (Apkarian et al., 2004a; Grisart & Plaghki, 1999). A possible reason for conflicting results has been attributed to instruments used to measure anxiety. When using a more pain-specific anxiety inventory correlations has been found (Grisart & Van der Linden, 2001), which suggest that these are better suitable for assessing a potential relation between anxiety and cognitive difficulties.

The prevalence of sleep problems ranges between 55% to over 90% in chronic pain patients (Morin, Gibson, & Wade, 1988; O'Donoghue, Fox, Heneghan, & Hurley, 2009), and sleep problems and fatigue may be an important factor contributing to cognitive difficulties. Cote & Moldofsky (1997) found poorer cognitive performance in fibromyalgia patients in computerized cognitive tasks compared to healthy controls. These findings were attributed to daytime sleepiness and self-reported fatigue, since the fibromyalgia patients were significantly more in stage 1 sleep according to polysomnography and thus had poorer sleep quality, and reported more fatigue, sleepiness, pain intensity and negative mood.

### **Interaction between several variables heightens perception of pain intensity**

In addition to having an effect in itself, one has to consider that variables of emotional distress, such as anxiety and depression, may have an additive effect on pain and cognitive function. It has been proposed that comorbid depressive symptoms in fibromyalgia patients may be influential on cognitive dysfunction because it lowers the threshold for experiencing pain (Aguglia, Salvi, Maina, Rossetto, & Aguglia, 2011), thus contributing to reports of higher level of pain intensity in these patients. Crombez, Eccleston, Baeyens, Van

Houdenove, & Van Den Broeck (1999) found that pain intensity by itself did not affect performance on a numerical interference task, the interference were best predicted by the interaction between pain intensity and pain-related fear, which could not be accounted for by negative affect.

The tendency to catastrophize correlates with attention towards pain (Roelofs, Peters, & Vlaeyen, 2003) and greater vigilance toward bodily sensations (Peters, Vlaeyen, & Van Drunen, 2000). This hypothesis has been confirmed by functional imaging studies where heightened activity was shown in medial frontal cortex and cerebellum, related to anticipation of pain, the dorsal anterior cingulate cortex and dorsolateral prefrontal cortex relating to attention towards pain, and claustrum, which is connected to amygdala relating to emotional aspects of pain. Together this shows that pain catastrophizing might influence pain perception through anticipation and increasing of attention towards pain, as well as heightening of emotional responses to pain, and that this results in changes of related areas in the central nervous system (Gracely et al., 2004).

Although not entirely consistent, these findings indicate that physical and psychological factors have an important mediating role in perceived cognitive difficulties and performance on neuropsychological tests. The interrelationships among the variables that potentially mediate the association between psychological distress and cognitive impairment needs to be explored with more large scale studies that use multi regression analysis to systematically study the contributions of the various factors on cognitive function.

### **Medications**

The effect of medications on cognitive function is an important possible confounding variable that needs to be considered. The literature on the effect of medications on cognitive functions in chronic non-malignant pain has shown mixed results. While some find no specific effect (Kurita et al., 2012), other findings indicate that medications may affect



cognitive function negatively, at least in some cognitive functions such as working memory (Sjøgren, Olsen, Thomsen, & Dalberg, 2000; Sjøgren et al., 2005). Some have shown that opioids improve cognitive function (Tassain et al., 2003; Dick et al., 2008). At present there are limited conclusions that can be drawn on the existing evidence (Kendall, Sjøgren, Pimenta, Højsted, & Kurita, 2010), but the use of medications need to be taken into account, as most of the studies report this as their greatest limitation. Of the studies in Table 1, there were only three studies that adequately controlled for medications by including a non-medicated control group (Landrø et al., 2013; Schiltewolf et al., 2014; Sjøgren et al., 2005). The most recent study found additional cognitive impairment in chronic low back pain patients receiving long-term opioid therapy in functions such as working memory, mental flexibility and spatial memory (Schiltewolf et al., 2014). While some included patients that currently were not taking medications (Antepohl et al., 2003; Park et al., 2001;), others statistically controlled for medications (Karp et al., 2006; Lee et al., 2010; Oosterman et al., 2010). The inclusion of a non-medicated group may not be possible because of ethical considerations (Moriarty et al., 2011). However, the effect of medications on cognition deserves more focus, and future research should consider using longitudinal studies to explore if cognitive function worsens over time, or if possible impairments due to medications are reversible.

### **A common factor underlying deficits in chronic pain**

Findings indicate that cognitive impairment in chronic non-malignant pain cannot be considered an epiphenomenon, and that impairments exist independently of confounding variables. Further, findings indicate that executive functions are the main area of impairment. It has earlier been stated that there seem to be no obvious pattern of cognitive impairments in chronic non-malignant pain (Moriarty et al., 2011). Some pattern has been observed, and the literature has proposed some candidates for underlying deficits. As mentioned in earlier

sections, among these are deficits in executive control, declined processing speed (Veldhuijzen et al., 2012) and maintenance of a memory trace (Dick & Rashiq, 2007). Exploring if such a pattern is evident is important for treatment possibilities of these cognitive symptoms.

### **The role of interference in the chronic pain literature**

This review shows that distraction is a central component of cognitive impairment in chronic non-malignant pain (Leavitt & Katz, 2006; Miró et al., 2011; Verdejo-Garcia et al., 2009). The many studies included here find that interference by distraction is crucial, and that attentional or memory functions are intact when in ideal conditions. Leavitt & Katz (2006) showed that when including a source of stimulus competition, the patients lost encoded information at a rate 44 % greater than an age-matched group with memory problems, and almost 3 times greater than the normative sample. This loss of information was disproportionately large compared to when the distracting stimuli was not included, as well as compared to the control group where the loss of information happened in a more gradual fashion when more distraction was included. Miró et al. (2011) also showed this interference effect, where patients were impaired on tasks consisting of an element of distraction that equally competed for attention. Using Posner & Rothbarts (2007) theory of attention they found impairments in executive control reflected in reduced performance on tests when an element of distraction was included. Further, they showed reduced vigilance reflected in slower overall reaction time, and greater alertness with higher reduction in errors after a warning cue. Verdejo-Garcia and colleagues (2009) found reduced cognitive performance on abstraction and distractibility measured by the WCST and IGT in patients with fibromyalgia. Of particular interest is the finding that fibromyalgia patients had poorer performance in number of categories and higher percentage of non-preservative errors. It has been confirmed from computational models that lower number of categories reflect a reduced ability for rule

detection, and increased non-preservative errors reflects mental flexibility and increased distractibility (Kaplan, Şengör, Gürvit, Genç, & Güzeliş, 2006).

### **Interference relate to executive control**

The findings of impairments due to interference support a hypothesis of deficits in executive control functions. The terms “inhibition” and “interference” are often used interchangeably in the literature, and as pointed out by some researchers, the term “interference” should be used when describing the empirical phenomenon when performance decreases (compared to baseline) because of processing of some irrelevant information for the task at hand. The term “inhibition” on the other hand, should be used as a theoretical mechanism that can explain interference findings (MacLeod, 2007). As stated by Klein and Taylor (1994) “There is a danger of circularity whereby investigators attribute interference effects to inhibition and subsequently define inhibition on the basis of behavioural interference” (p. 146). From this author’s point of view, when dealing with distraction and interference, a crucial element is the ability to inhibit such interfering stimuli. Although studies refer to “interference deficits” in the chronic pain literature, a central element in cognitive impairment in chronic pain conditions may be the inability to inhibit prepotent responses when facing distracting stimuli. This serves as evidence for a central and specific underlying dysfunction in executive control in chronic non-malignant pain.

### **Executive memory functions support executive control hypothesis**

This topical review shows that executive deficits are reflected in the research on memory functions. Memory is to a large degree affected by executive functions, and when using only global indicators of memory function, the whole picture about the nature of impairment is not captured. The findings in the area of executive memory functions are also in line with an executive control hypothesis. When examining the “memory deficit profile” of chronic pain patients, memory impairments are found in memory functions related to

attentional factors modulating and controlling the efficiency of memory functioning rather than to the memory process itself (Grace et al., 1999). This executive control component in memory functions has been addressed in neuropsychological literature of executive functions (Miyake & Shah, 1999). This is further shown in research on effortful processing in episodic memory and semantic memory, where impairments are found in long-term memory recall tasks requiring sustained effort, but no impairments in tests of short-term memory (Landrø et al., 1997). The deficit seems thus not to be in short-term storage, but rather in managing and controlling competing information, which is an important executive control function. That impairment is not reflected in global measures are also supported by studies using a recognition-familiarity paradigm. Chronic pain patients show a pattern of decreased recollection and increased sense of familiarity during memory tasks. These findings support that demanding tasks are more disrupted, as well as the hypothesis that memory deficits are caused by attentional or executive factors (Grisart, Van der Linden, & Bastin, 2007). Findings in the area of working memory show that significantly reduced non-verbal working memory and impaired non-verbal long-term memory is evident in free recall, while recognition seems not to be affected in chronic pain. This strongly indicates that it is management and control, rather than storage that is impaired (Luerding et al., 2008).

Multiple studies finding intact working memory or short-term storage, have been conducted in ideal conditions without distractions, which cannot be said to reflect our everyday complex environments (Leavitt & Katz, 2006). The same argument can be used on subjective reports, and the discrepancy between subjective reports of cognitive difficulties and deficits found using performance-based neuropsychological tests. Few studies use well-validated questionnaires measuring self-reported cognitive dysfunction. The ones that find support for accuracy use self-report measures of cognitive difficulties with high ecological validity relating to everyday situations often experienced by this patients group (Glass, 2005;

Landrø et al., 2013). The patients often report problems with memory, but in reality the factor that may be compromised seems to be executive functioning, and for example encoding material when distracting elements are present. Transferring this to everyday situations may reflect how this is related; in work or in social situations there are often many aspects that one has to pay attention to, as for example planning and executing appropriate behavior. What may manifest itself as perceived memory problems, may when deconstructed be problems with encoding the topic of conversation when also paying attention to other elements in the situation, or trouble remembering specifics when doing multiple things at the same time.

Specifically interesting in the context of this review, is the finding that when using a valid self-report questionnaire reflecting everyday difficulties such as Everyday Memory Questionnaire (Sunderland, Harris & Baddeley, 1983), perceived cognitive difficulties correlate with tests of executive control, but not working memory (Landrø et al., 2013). Together this point to executive control deficits as central in both perceived cognitive difficulties and impairments found using neuropsychological tests. Further, both questionnaires and neuropsychological tests with high ecological validity are in line with the management and control of interfering stimuli as a central deficit in chronic non-malignant pain and should be used in further research in this area.

### **Neural correlates support a theory of executive control**

Neural data on cognitive control mechanisms as central for neuropsychological deficit in chronic non-malignant pain is considered sparse (Mercado et al., 2013). The existing evidence does support inhibition as a possible underlying mechanism. Glass (2011) found that chronic pain patients show altered cortical activation during the executive inhibition tasks. When performing a simple Go/No-Go task, no differences were found between patient group and healthy controls in either time or in accuracy. A simple go/no-go task which were not likely to show differences were chosen on purpose, to be able to compare different levels

of effort or neural processing. The patients showed less activation in the inhibition network and attention network, and more activities in other areas not normally part of these networks (Glass et al, 2011). In another study, participants completed an emotional Stroop-task while ERPs were recorded. While behavioural outcomes did not show significant differences, ERP data showed clear between-group differences. Fibromyalgia patients showed faster reaction rates and higher error rates compared to controls. This can be considered a more poorly controlled reaction with more impulsive reactions. A hypothesis is that patients activate top-down attentional control processes to compensate and keep behavioural outcomes at an acceptable level, while on a neurological level this compensation is evident through excessive activation (Mercado et al., 2013). This is in line with the neurocognitive model of pain and attention (Legrain et al., 2009), and a top-down executive control as central of cognitive impairment.

### **Executive control over nociceptive stimuli**

An important note from the neurocognitive model of pain and attention (see Figure 1) is that attentional control over pain is not only dependent by disengagement of attention away from the nociceptive stimuli, but that top-down control over attention is possible through the attentional load and attentional set features (Legrain et al., 2009). This executive control may guide selective attention according to higher-order goal priorities, and therefore make sure that attention is maintained on pain-unrelated information. As presented earlier, the top-down modulation and attentional load hypothesis propose that patients may have difficulties with executive control over nociceptive interference. Another possibility is the combination of top-down and attentional set hypothesis, where hypervigilance or over-attentiveness towards pain and pain-related information is an important factor. Hypervigilance is a goal-dependent attentional process, and can be considered unintentional and efficient (Crombez et al., 2005), and patients may have excessive expectations or attention to bodily signals in their attentional

set. According to this, when attention to pain is considered goal-relevant activity, the patients then should have difficulties with, or an inability to inhibit nociceptive intrusions in working memory (Legrain, Iannetti, Plakhi & Mouraux, 2011).

As a general rule, the processing of intrusive nociceptive signals interferes with processing of other stimuli, and selective attention is activated when the competition between different interfering stimuli exceeds processing capacity limits (Legrain et al., 2011). The ability for executive control or inhibition of stimuli is dependent upon higher-order goals present in working memory. This may aid in explanations of deficits in executive control in chronic non-malignant pain. As an example, it may explain findings that patients with chronic pain have difficulties with cognitive tasks requiring management of distractions. With low interference from these distracters, both stimuli can be processed. Keeping the model by Legrain et al. (2009) shown in an earlier section mind (see Figure 1), the strength of top-down modulation may correspond to the extent a person is capable of executive control over pain-related and pain-unrelated interferences. Executive control thus stand out as a central candidate for an underlying process that may be disrupted in chronic non-malignant pain.

### **Additional insight due to experimental studies**

One way to gain additional insight on executive control as a possible underlying process is experimental studies. Experimental studies have found that overlapping cognitive resources play an important role in both pain processing and executive working memory. An experimental study calibrated pain intensity individually for participants, while they performed a demanding executive task (3-back task), and findings showed that variations in pain fully explained decreased performance (Buhle & Wager, 2010). It is also shown that when healthy adults were tested on the Stroop task while performing a cold pressor test, findings indicated a unique association between ability for cognitive inhibition and immersion

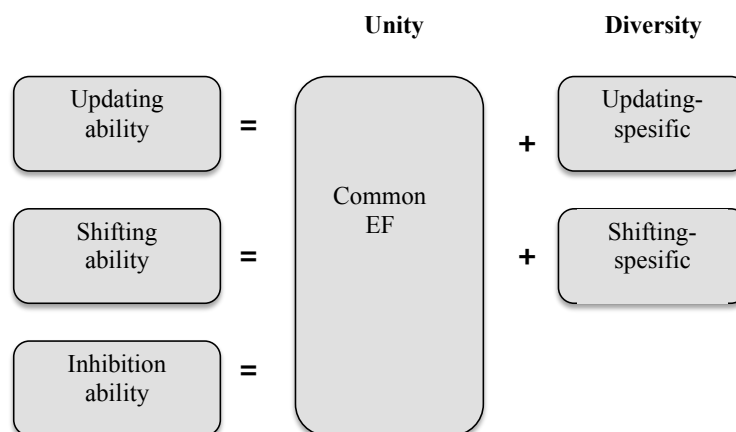
time on the cold pressor test, pain intensity and unpleasantness. An association were not found in other aspects of executive function, indicating a specific role for cognitive inhibition (Oosterman et al., 2010). Further, it is found that individuals with a stronger ability for response inhibition measured by a stop-signal task are better able to inhibit escape and avoidance behaviors related to pain (Karsdorp, Geenen, & Vlaeyen, 2014). This is in line with Oosterman et al. (2010), but can be considered strengthened evidence, using a stop-signal task (Logan & Cowan, 1984), which may be a more pure measure of cognitive inhibition than the Stroop-paradigm (Miyake et al., 2000). The findings suggest that individuals with a stronger ability to inhibit responses in a stop-signal task are better able to inhibit or escape avoidance responses elicited by pain, when other highly relevant goals are present (Karsdorp et al., 2014). This is in line with the neurocognitive model of pain presented by Legrain et al. (2009), and that selective attention is dependent on executive control processes (Legrain et al., 2011).

### **A common underlying factor in executive functions**

The findings of a central role for executive control in chronic pain can be considered in line with theoretical frameworks of executive functions. Executive functions are non-unitary and considered a family of functions, and the moderately high inter-correlations among the three most commonly tested executive functions (inhibition of prepotent responses, updating working memory and switching) raises an important question about the nature of the sources of commonality in executive functions (Miyake et al., 2000). Taking the issue of unity and diversity one step further, a central question is what specific ability each executive function components are tapping. To examine the cognitive and biological underpinnings of the unity and diversity, it has been attempted to decompose what is common and what is unique to the specific ability. Findings indicate that updating and shifting abilities show unique variance in addition to correlating with a common executive factor. Inhibition on the



other hand, loads perfectly on the common executive function factor. This has been replicated in several populations (Friedman et al., 2008; Friedman, Miyake, Robinson & Hewitt, 2011). One interpretation is that inhibition in fact is central as an underlying factor of commonality in executive functions, at least when using broader definition of inhibition (Friedman et al., 2008).



*Figure 4.* The figure by Miyake & Friedman (2012) shows the unity and diversity of executive functions. On the left side of the equation, the three most common executive functions are shown. On the right side of the equation, it is shown that when extracting what is common in the three factors, the inhibition ability is isomorphic to the common factor.

### **Difficulties with inhibition-related functions**

It is important to keep in mind that although executive control might be central in dysfunction presented in chronic non-malignant pain, the picture may not be that simplistic. The chronic pain literature has addressed a need for studies that divide cognitive inhibition into smaller domains, and further studies with a multi-perspective approach to inhibition in decreased memory performance (Veldhuijzen et al., 2012). Conceptual confusions are evident in definition and measurement of inhibition (Friedman & Miyake, 2004). Both the task impurity problem and problems with construct validity on neuropsychological tests of inhibition are relevant. No tasks are pure measures of cognitive inhibition, since inhibition

always involves inhibition of *something*, and thus inhibition also involves other processes (Friedman & Miyake, 2004, Shilling, Chetwynd, & Rabbit, 2002). A central critique of research on cognitive inhibition is the tendencies of researchers to often use tasks they believe measure inhibition, without adequately address the question of what the tests actually measure. This may be an important reason that some do not find evidence for difficulties in executive control in chronic pain patients. Researchers have used various methods to alleviate these problems, some using a latent variable analysis mentioned earlier (Friedman & Miyake, 2004; Miyake et al., 2000), while others have tried to make the tasks used as similar as possible (Shilling et al., 2002). The different ways of solving this problem statistically do however have many difficulties. Making tasks as similar as possible is problematic since many findings where inhibition-related functions are used as an explanation for dysfunction, the findings can also be explained by other processes (Friedman & Miyake, 2004; MacLeod, Dodd, Sheard, Wilson, & Bibi, 2003). Therefore, studies that find evidence for inhibition as a central underlying process for executive function and dysfunction in chronic pain may be confounded, and when it comes to inhibition as a common underlying process in executive functions, the picture may also not be so simplistic.

### **Other possibilities for central deficits in chronic pain**

Not all studies agree that inhibition might be underlying impairment. A study comparing fibromyalgia patients to healthy controls on the Stroop Color-Word Test (SCWT) and the Multi-Source Interference Test (MSIT) found inhibition to be intact, but found evidence of declined processing speed (Veldhuijzen et al., 2012). In the results however, the patient group performed worse on both inhibition tests, but to a similar degree in neutral condition and in interference condition. No significant interaction between test and group, condition and group, or test, condition and group were found, which indicated that the patients had a general tendency for poorer performance. The authors therefore concluded that

the impairment seen in these patients are not specific to cognitive inhibition, but rather that the speed must be the underlying process that is impaired. The authors hypothesized specifically the ability to retrieve information during learning to be sensitive for interference, while the ability to inhibit may not be compromised in these patients.

Others have found no evidence of dysfunction in processing speed, but poorer performance on a broad array of other cognitive measures in the same sample (Park et al., 2001). Impaired processing speed known to be a commonly found deficit in depression (Veiel, 1997), and the amount of depressive symptoms varies greatly in these studies. In Park et al. (2001) subjects were screened for depressive symptoms prior to the study, and further excluded if presenting symptoms in a clinical range. This was not evident in Veldhuijzen et al. (2012), and differences in depressive symptoms can be considered as a possible factor explaining the opposing results. In general, this shows the importance of recruitment strategies and characteristics of the sample of participants studied.

Other reasons that some studies show contradicting findings regarding the role of interference and pain are both conceptual and technical. This includes type and intensity of the cognitive task demand, and the degree of temporal overlap between the cognitive task and pain processing. The task must substantially and continuously demand executive resources. One should compare tests using executive working memory tasks such as the n-back task, and working memory tests that only involve storage, such as Sternberg tasks. Then the role of control mechanisms in working memory will be evident (Buhle & Wager, 2010).

### **General limitations**

A great limitation in the field of cognitive impairment in chronic pain is that one needs to consider that there are factors that cannot be accounted or corrected for in a testing situation. Two persons may have the same score on the neuropsychological tests, but have different scores on the subjective self-report measures, and this may also be seen in the test

situation. Some may be insecure, make guesses, while others may be confident or overconfident on their functioning. This is an important point relating to the fact that the experience these people have in their real life is valid even though not always perfectly reflected in the test situation. Also, as mentioned earlier, some may “rise to the occasion”, and performance may be good in this particular situation (Ambrose et al, 2012). This may cause more feelings of exhaustion, and be a one-time performance, which is not how we function in everyday life. Also, a test score reflects maximum performance, and there is room for error in that the findings will be confounded by amount effort invested. A solution might be to use a test that shows how research participants relate to the feedback. This might be a good paradigm to observe “overachieving” or “rising to the occasion”, and give a more ecological valid results reflecting everyday life. Test-related fatigue is an important variable to consider, and some also make the point that it would be interesting to do repeated measures in following days, to see if patients get fatigued by rising to the occasion (Dick et al., 2008).

### **Cognitive impairment in different pain syndromes**

Studies that have examined cognitive performance in mixed chronic pain disorders does not provide information on whether specific impairments are more frequently observed in specific disorders (Moriarty et al., 2011). Findings indicate that there are differences between subgroups. A study showed that every third of patients with neuropathic and generalized pain scored below cutoff for clinically significant cognitive impairment, while this was not evident in localized pain patients (Landrø et al., 2013). Some would argue that these differences are due to amount of pain, or pain intensity, but these groups did not differ in variables such as reported pain last week or pain intensity. Apkarian and colleagues (2004a) found patients with chronic pain were impaired in emotional decision-making, measured by the Iowa Gambling Task. They did not find any other impairment in their population, not in attention, short-term memory or general intelligence. They interpreted this

as chronic pain being associated with a specific deficit, which impact everyday life especially in risky, emotionally laden situations. Further, group differences were found between patients with CBP and CRPS, and since the groups had the same level of pain intensity, these differences could not be explained by amount of pain. This opens up for an interesting question about similarities and differences of different chronic pain conditions with different etiologies.

### **Chronic pain and changes in the brain**

A central question related to this is if the structural changes in the brain are a cause or a consequence of chronic pain. It has been hypothesized that chronic pain may alter the structuring of the brain, as studies show local morphological alterations in anterior cingulate cortex (ACC), orbitofrontal cortex, insula and dorsal pons, which are areas known to be important for pain regulation. These alterations overlap in these areas, therefore pointing towards a common “brain signature”, however, the alterations have distinct features for different pain syndromes (May, 2008). This is confirmed by studies showing that chronic pain patients have reduced gray matter density in dorsolateral prefrontal cortex (DLPFC) and in the right thalamus, that is strongly related to pain characteristics in a pattern distinct for neuropathic and non-neuropathic chronic back pain (Apkarian et al., 2004b). There thus seems to be overlapping but still distinct patterns of dysfunction. This is supported by brain imaging studies, which indicate that neuropathic pain may have a larger impact on the brain than other chronic pain conditions. In studies of neuropsychological performance, patients with neuropathic pain without these comorbid anxiety and depression symptoms show a significant higher level of impairment than groups of mixed chronic pain patients presenting with anxiety and depression. Impairments have found to be almost twofold of the impairment found in the mixed groups (Povedano et al., 2007). This show that cognitive impairment is prevalent to a high degree in patients with neuropathic pain, and further indicates that type of

pain might have a distinct effect on cognitive function, with distinct mechanisms of pain affecting cognition in distinct ways. As commented by earlier reviews (Moriarty et al., 2011), there is a need for comparative studies across chronic pain disorders, to establish whether impairments are indeed pain-related or whether they are a consequence of other disease characteristics.

### **Are cognitive dysfunctions reversible?**

When it is established that patients with chronic non-malignant pain have impairments in executive functions, the next important question is how to best treat these impairments. Common arguments has been that treatment targeting pain intensity as well as treating comorbid conditions such as disorders of anxiety and depression, sleep problems or fatigue will alleviate cognitive deficits (Suhr, 2003). What has been attempted established in this review is that cognitive impairments exist independent from such symptoms, and that deficits found are related to more specific cognitive functions than previously thought. A new and important question therefore arises if these impairments are reversible and can be targeted through cognitive training programs.

Evidence for the effectiveness of attention training in other patient groups exists (Cicerone et al., 2000; 2011). Central in cognitive training literature are questions about the transfer effects from abstract training tasks to everyday complex environments in cognitive training programs. A large-scale study including 11,430 participants found no transfer effects of cognitive training even on closely related cognitive tasks (Owen et al., 2010). Some have found that attention and working memory training have no significant effect on performance on neuropsychological tests, but on perceived cognitive difficulties (Mäntynen et al., 2014). Others have found that cognitive training of a broad array of tasks show transferable effects on measures of fluid intelligence, and that this effect is dosage-dependent (Jaeggi, Busschkuhl, Jonides, & Perrig, 2008). Interestingly from this review's point of view, are

findings that intensive high-demanding working memory training show transferable effects to cognitive control-processes used in real-world cognition. As previously mentioned, are executive functions closely tied to the ability for self-regulation (Solberg-Nes et al., 2009). Interesting studies on rumination in depressed patients have found that depressive rumination is associated with an inability to inhibit previously relevant information, rather than switching from old to new information (Whitmer & Banish, 2007), and this exemplifies the strong link between executive function and self-regulation, and show how this executive control deficit may be central in several common symptoms in chronic pain.

To days date, the literature on cognitive training in chronic non-malignant pain remains sparse. Future research should address the question if specific high-demanding cognitive training programs targeting cognitive control processes may alleviate executive control deficits in this patient group. How demanding these cognitive training tasks are seem to be central, and transfer effects are dependent on continuous training at maximum performance level. Importantly, the nature of the tasks should target executive control processes (Schweizer, Hampshire, & Dalgleish, 2011).

### **Implications and future directions**

As noted by earlier reviews, there are a lot of methodological shortcomings and a high risk of bias in this area of research (Berryman et al., 2013). As a central point, there is a need for research that systematically include all potential confounding variables, including depression, anxiety, pain catastrophizing, sleep problems, fatigue and medications, which all show evidence of affecting cognitive functions. Intriguing findings also exists for the role of body awareness, or the hypervigilance for bodily signals. In addition, studies that measure cognitive functioning by performance-based neuropsychological tests should include variables such as effort. These should include well-validated questionnaires for subjective reports to compare the self-reported cognitive difficulties and performance on

neuropsychological tests. Further, studies should compare different subgroups of chronic pain, such as neuropathic and generalized pain conditions. This to explore if they present with different neuropsychological profiles which can be attributed to pain etiology or mechanisms of pathophysiology, as brain imaging studies show interesting differences. Related to this, more studies combining brain imaging and neuropsychological testing could give important insights, as it already has shown interesting results (Glass et al., 2011; Veldhuijzen et al., 2012). These findings have important implication for treatment of this patient group. If impairments in executive control is a central underlying deficit, it would be interesting to do a longitudinal study with repeated measures, to see if high-demanding working memory training would have an effect on executive control processes.

As evidenced through reviewing the literature, there is a lack of research that is guided by basic neuropsychological theory and theories of pain and its effect in attention. Executive functioning is a concept that is proven elusive to define (Jurado & Rosselli, 2007) and difficult to measure (Miyake et al., 2000), and this has negative implications for research. In the area of cognitive function in chronic pain, it may have resulted in a tendency to conduct research that only touch the surface of what is the nature of cognitive impairment in this patient group, and this has further been complicated in that chronic pain is a multidimensional phenomenon presenting with multiple composite problems, such as anxiety, depression, sleep problems and fatigue in addition to pain. When seeing findings in the light of neuropsychological theories on executive functions, there seems to be a tendency towards inhibition-related functions as a common underlying process that is disrupted. This is supported by the findings that patients with chronic pain show impairments with increasing cognitive demand, a theory named the limited resource theory (Eccleston & Crombez, 1999; Moriarty et al., 2011). The mechanism by which this happens is abilities in inhibition-related functions, presenting itself as executive control, exemplified by the ability to inhibit



nociceptive intrusions in working memory (Legrain et al., 2011). This is dependent on higher-order goals, but it also relates to goal-independent factors. This relates to a top-down and bottom-up division of attentional capture. The strength of the top-down mode is dependent on the ability for inhibition. This is supported by basic neuropsychological theory on executive function, which suggests that inhibition-related function serves as a common underlying executive factor (Miyake et al., 2012).

The study of underlying cognitive process or mechanisms in this field should to larger degree use methods from cognitive science, where mechanisms are studied by manipulating some part of cognitive tasks to examine the effect of this manipulation on performance. This should be used in addition to brain imaging methods. In these paradigms one can compare different levels of interference, and different stages of memory, for instance storage and retrieval (Glass, 2009). This has been an increasing trend in experimental studies, and should be used in a larger degree in clinical studies. Experimental studies have given valuable insight. Still, some will argue that it gives a wrong and simplified view of pain effects on cognition by reducing the effect of the motivational-affective and evaluative dimensions of pain. In addition, it does not take into account the possible cumulative effect of pain on cognition (Gagliese, 2007; May, 2008).

### **General summary**

This topical review has shown that executive impairments are central in chronic non-malignant pain. This conclusion can be made not only on research using standard executive tests, but also in the areas of attention and memory functions. This is possible when reviewing the existing research in the light of models of executive functions that point to the unity and diversity of different components of executive functions such as updating working memory, shifting between mental set and inhibition of pre-potent responses. This topical review is an attempt to extract what process may underlie the cognitive impairments found in

non-malignant chronic pain. Possible candidates have been both global and specific deficits. Here a common underlying process of executive control is presented. The term underlying process is chosen, as it best relates to the neuropsychological literature on the nature of executive functions. A deficit in executive control mechanisms fits with patient reports of difficulties managing complex everyday environments, as well as difficulties with self-regulation. This is also in line with basic neuropsychological theory about unity and diversity of executive functions and the hypothesis of a common executive factor, theories on pain and its effect on cognitive function, and neural correlates of pain and its effect on the brain.

Limitations are also evident in this study. It can be claimed that this topical review only focuses on one aspect of cognitive functioning, as it is limited to aspects of executive functions. It is as emphasized earlier, important to include studies both in the area of multiple memory and attentional functions to adequately illustrate how impairments found in different aspects of cognitive functions may relate to deficits in executive functions. Further, a considerable amount of studies on this topic is conducted on fibromyalgia. As mentioned in earlier sections, there may be differences in cognitive impairments in different pain syndromes, and building an argument of executive control as an underlying deficit solely on one diagnostic group that in addition is commonly associated with multiple symptoms other than pain, is not to be preferred. This topical review has thus emphasized the inclusion of several chronic non-malignant pain syndromes. There are also methodological limitations in this study. Several search databases should have been used, as well as a more strict and systematic review criteria, as stressed in initially in this review. This author believes that the strength of this review have been the continuous tying of empirical findings to theoretical frameworks, from both basic neuropsychological literature and on pain and its effects on attention. Together, this topical review should help guide further research on the possibility for executive control difficulties as a basic underlying deficit in chronic non-malignant pain.

### **Conclusions**

This topical review shows that cognitive impairments in chronic non-malignant pain are associated with impairments in executive functions. The impairments are in line with a specific impairment in a common underlying process related to the ability for executive control over pain-related stimuli, as well as distracting personal and emotional information. This is in line with patient reports, and reflects the challenges of a complex everyday environment. Future research should try to specifically target executive control through high-demanding working memory training programs aiming at cognitive control processes.

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