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Executive Functions and Pain

A Systematic Review

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Abstract: A growing body of literature suggests that chronic-pain patients suffer from problems in various neuropsychological domains, including executive functioning. In order to better understand which components of executive functioning (inhibition, shifting and/or updating) might be especially affected by pain and which mechanisms might underlie this association, we conducted a systematic review, including both chronic-pain studies as well as experimental-pain studies. The chronic-pain studies ($N = 57$) show that pain is associated with poorer executive functioning. The findings of experimental-pain studies ($N = 28$) suggest that this might be a bidirectional relationship: Pain can disrupt executive functioning, but poorer executive functioning might also be a risk factor for higher vulnerability to pain.

Keywords: executive functioning, inhibition, shifting, updating, pain

Exekutivfunktionen und Schmerz, eine systematische Übersichtsarbeit

Zusammenfassung: Eine Vielzahl von Studien weist darauf hin, dass chronische Schmerzpatienten in ihren neuropsychologischen Leistungen, u. a. den Exekutivfunktionen, beeinträchtigt sind. Um besser zu verstehen, welche Komponenten der Exekutivfunktionen (Inhibition, kognitive Flexibilität und/oder Arbeitsgedächtnis) besonders betroffen sind und wie sich der Zusammenhang zwischen Schmerz und Exekutivfunktionen erklären lässt, haben wir die empirischen Befunde zu chronischen als auch zu experimentellen Schmerz in einer systematischen Übersichtsarbeit zusammengetragen. Studien zu chronischen Schmerzpatienten ($N = 57$) zeigen, dass chronischer Schmerz mit milden Einbußen in den Exekutivfunktionen einhergeht. Die Befunde aus experimentellen Schmerzstudien ($N = 28$) deuten darauf hin, dass der Zusammenhang zwischen Schmerz und Exekutivfunktionen sogar bidirektional ist, das heißt: Schmerz interferiert/stört die Exekutivfunktionen und beeinträchtigte Exekutivfunktionen wiederum können ein Risikofaktor für eine erhöhte Schmerzvulnerabilität sein.

Schlüsselwörter: Exekutivfunktion, Inhibition, kognitive Flexibilität, Arbeitsgedächtnis, Schmerz

More than one-third of people worldwide suffer from chronic pain (Fayaz et al., 2016; Tsang et al., 2008). It is widely acknowledged that chronic pain not only leads to emotional suffering, but can also have a negative impact on neuropsychological functioning (Hart et al., 2000; Moriarty et al., 2011). One domain of cognition that has been repeatedly found to be affected by pain is executive functioning (Berryman et al., 2014; Moriarty et al., 2011). Executive functions are described as higher-order skills that enable an individual to regulate actions and thoughts during goal-directed behavior. They can be seen as an umbrella term to encompass a variety of quite heterogeneous cognitive processes (Friedman & Miyake, 2017). To break executive functions down into more homogeneous components, Miyake and colleagues (2000) suggest three different components: information updating and monitoring (“updating”), mental set shifting (“shifting”), and inhibition of prepotent responses

(“inhibition”). Whereas updating refers to on-going task monitoring and online adjustments, shifting is the ability to switch attention between different task demands. Inhibition relates to an individual’s ability to exert control over prepotent responses, which are reflexive and automatic responses that need conscious, top-down control in order to be suppressed. Although additional executive functioning components have been postulated (Fisk et al., 2004), these three components have been used most frequently (Jurado & Rosselli, 2007).

First evidence for a link between pain and executive functioning stems from clinical studies (Armstrong et al., 1997; Grace et al., 1999; Grisart & Plaghki, 1999). Here, the relationship between different components of executive functioning and pain is usually studied using two different study designs, namely by (1) group comparisons of executive functioning performance between pain patients

and pain-free healthy controls and/or (2) correlational approaches between executive functioning performance and self-reported pain intensity within a group of chronic-pain patients. Using both designs, evidence has been found in favor of as well as evidence against a link between chronic pain and executive functions. In order to draw conclusions, all empirical evidence has to be gathered in a systematic review or meta-analysis. So far, two meta-analyses by Berryman and colleagues (2013, 2014) have been conducted on this topic, which focused solely on group comparisons between patients and controls. It was reported that people with chronic pain show a small to moderate impairment in executive functioning performance compared to pain-free individuals. The question remains whether executive functioning problems worsen with higher pain intensity.

Our systematic review serves to close this gap and includes the empirical evidence on correlational analyses as well as group comparisons. Moreover, we gather evidence on the potential directions of this association. Is pain causing the executive functioning problems or might poor executive functioning precede the development of chronic pain – and even be a vulnerability factor for chronic pain? It is impossible to study the causal link using cross-sectional study designs in chronic-pain patients, though by experimentally inducing pain (e.g., using heat or pressure), it might be possible to study the direction of the association between executive functions and pain. Therefore, we also include experimental-pain studies in the current systematic review.

In experimental-pain studies, pain responsiveness is often measured by asking the participants to rate the intensity of the experimental pain stimulus or by measuring when participants start to feel pain (pain threshold) or how much pain participants can tolerate (pain tolerance) (Bjekić et al., 2017). One additional experimental pain model of interest in the context of executive functioning is the conditioned pain modulation paradigm, an experimental pain model to measure endogenous pain inhibition (Ickmans et al., 2015; Yarnitsky, 2010). The relationship between these different responses to experimental pain and executive functions is studied mostly using three different designs: (1) an interference design in which participants perform an executive task twice, once with and once without painful stimulation; (2) an interference design in which participants receive painful stimulation twice, once with and once without simultaneously performing an executive function task; and/or (3) a correlational approach in which executive functioning performance and pain responsiveness are assessed in two separate blocks. Whereas interference designs allow to draw more causal conclusions about interference effects of pain on executive functioning (or vice versa), correlational approaches help

to better understand whether poor executive functioning might be linked to high pain responsiveness.

In sum, this review provides a comprehensive overview of the findings on the relationship between executive functioning and pain by taking both chronic-pain studies and experimental-pain studies using various study designs into consideration. Regarding executive functions, we have attempted to organize the results into the three domains proposed by Miyake and colleagues (2000): updating, shifting, and inhibition. Considering that pain is omnipresent in the clinical field, we hope to create a useful review not only for researchers, but also for people working in the clinic.

Methods

Search Strategy

We conducted a systematic search of literature published through July 2018 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement Guidelines (Moher et al., 2015). We scrutinized the most appropriate electronic databases for this topic, namely, PSYCINFO and MEDLINE, via EBSCOhost with the following sensitive keywords relating to executive functioning: “executive function” or “cognitive inhibition” or “prepotent inhibition” or “response inhibition” or “cognitive control” or “stroop” or “anti saccade” or “antisaccade” or “anti-saccade” or “stop-signal task” or “stop signal task” or “set shifting” or “mental flexibility” or “attention switching” or “attention regulation” or “task switching” or “plus-minus task” or “plus minus task” or “number-letter task” or “number letter task” or “local-global task” or “local global task” or updating or “working memory” or “N-back” or “keep track task” or “letter memory task” or “tone monitoring task.” The above keywords were paired with the keyword pain. The search was further narrowed down to journal articles written in English that made use of a human adult population. Access to the search log can be granted on inquiry.

Study Selection

Only those articles were considered to be part of this systematic review if all relevant methods and measures (i.e., executive functioning tests, measures of pain responses, and/or pain induction methods) had previously been validated (e.g., tested for construct, criterion, or content validity). Moreover, studies had to provide a clear description of statistics. For chronic-pain studies, two types of

study designs were considered relevant: (1) a group comparison of executive function performance between chronic-pain patients and a healthy control group and (2) a correlational approach that assesses the correlation between executive functioning performance and self-reported pain intensity within a group of chronic-pain patients. For the experimental-pain studies, three types of study designs were considered relevant: (1) an interference design in which participants perform an executive task twice, once with and once without receiving painful stimulation, (2) an interference design in which participants receive painful stimulation twice, once with and once without simultaneously performing an executive function task and (3) a correlational approach in which executive functioning performance and pain sensitivity are assessed in two separate blocks and later correlated. The first interference design is conducted to investigate whether painful stimulation reduces executive function performance (pain → executive functioning), while the second interference design is conducted to investigate whether performing an executive functioning task reduces responsiveness to painful stimulation (executive functioning → pain).

Exclusion Criteria

Studies that measured executive functioning based solely on subjective self-report or observer ratings were excluded. Studies were also excluded when the executive functioning task was confounded by other tasks that had to be performed simultaneously (e.g., a distraction task) – with the exception of a simultaneous application of pain. If a neuropsychological test could not be assigned to one of the three domains proposed by Miyake (2000), or if test scores were compiled across different domains of executive functioning without reporting outcomes for the different domains separately, these studies were also excluded. For chronic-pain studies, we included only studies in which the patient group was suffering from diseases whose symptoms are strongly pain-related (e.g., fibromyalgia, migraine). Whiplash and chronic fatigue syndrome were excluded because these diseases have a weaker link to pain.

Study Selection Protocol

The results were exported to the citation management software Refworks (Proquest, Ann Arbor, Michigan, USA) and title screened for eligibility by one author (LP). Following the title screening, the abstracts were independently investigated by two authors (LP, SB). If there was disagreement, a group discussion was held (LP, SB, MK). After

the selection procedure, two systematic reviews by Berryman and colleagues (2014) and Moriarty and colleagues (2011) as well as the literature summary by Buhle and Wager (2010) were searched for additional articles relevant for the present review. Figure 1 shows the selection procedure with a PRISMA flowchart.

Information Extraction

We extracted the following information from each included study: type of pain (chronic pain and/or experimental pain), sample information (patients and/or healthy participants, mean age, number of participants), name of executive function test, cognitive domain reflected by the executive function test, type of study design (group comparison, correlational approach or interference design), and the outcome of the study (which executive tests showed significant associations with either chronic or experimental pain, the direction of this association and, if available, effect sizes [for group comparisons: mean values and standard deviation for the computation of the Glass' Δ effect size; for correlations: correlation coefficients]). For chronic-pain studies, we also extracted the mean pain intensity rating and the disease duration of the patient group. For experimental-pain studies, we also extracted the type of pain stimulus (e.g., heat, pressure) and the type of pain measure (e.g., intensity rating, threshold, tolerance, conditioned pain modulation, temporal summation). The information was extracted by one reviewer (LP) and independently counterchecked by a second reviewer (SB).

Risk of Bias Assessment

To assess the quality of the studies and the risk of bias, we graded the studies based on the following criteria (adopted from the Newcastle Ottawa criteria; Wells et al., n.d.), (1) information about the sex distribution and age of the participants, (2) a study population that represents the true population, (3) a screening for psychiatric disorders, (4) specification of executive function tests, (5) specification of type of pain stimulus in case of experimental pain and a diagnosis according to the accepted criteria in case of chronic pain, (6) in case of chronic pain, control for age and education in the between-group comparison, and (7) in case of chronic pain, report of analgesic medication use. Each criterion was judged as either *successfully fulfilled* (1), *partially fulfilled* (0.5), or *not fulfilled* (0). The maximum score for experimental-pain studies was 5. For chronic-pain studies, the maximum was 6 (correlational design) or 7 (group comparisons).

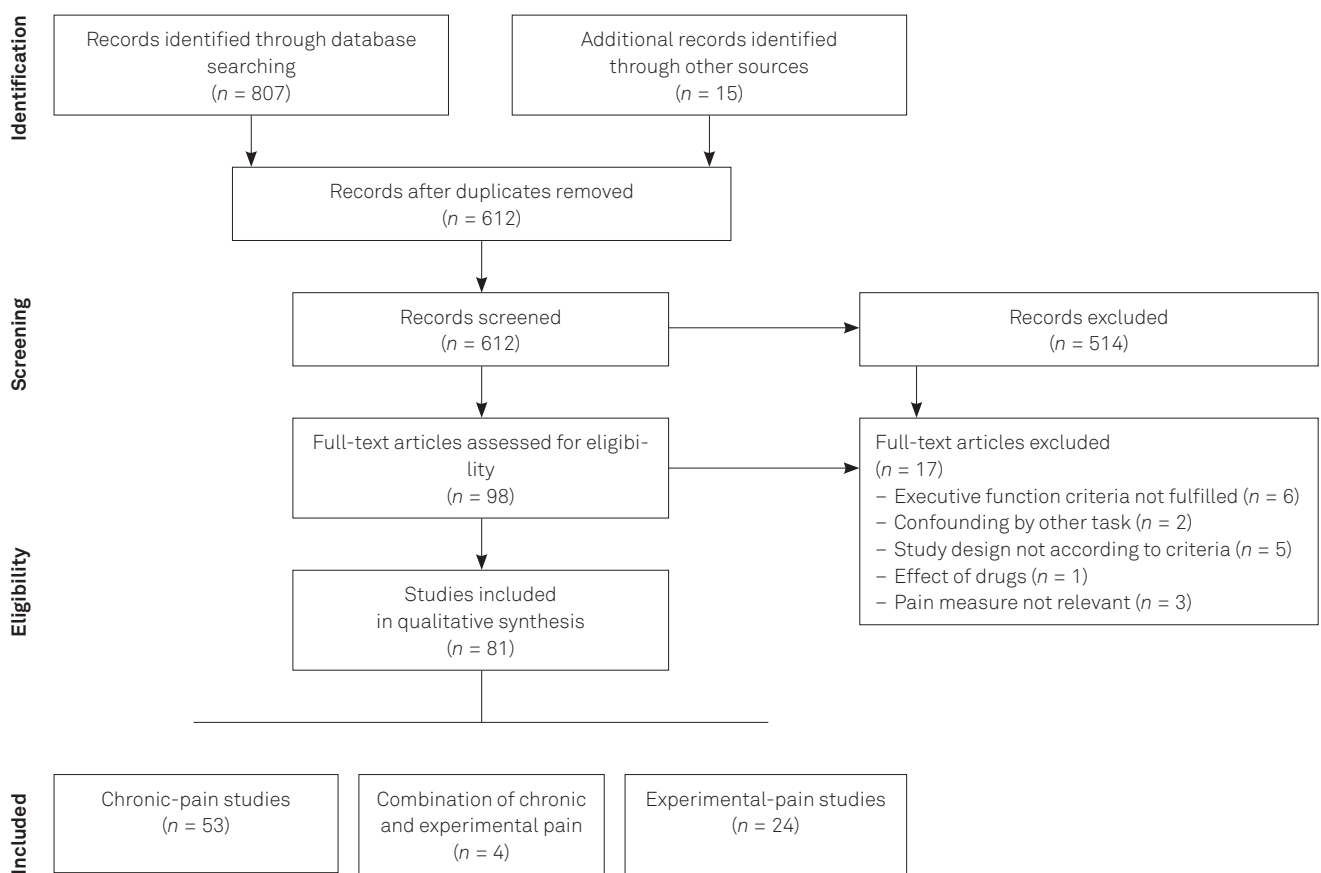


Figure 1. PRISMA (preferred reporting items for systematic review and meta-analysis) flow diagram.

Results

The initial literature search identified 807 studies with 15 additional studies found through manual searching of reference lists (see Figure 1). After excluding duplicates and screening the remaining titles and abstracts, 98 studies remained. Seventeen articles were excluded after reviewing the full text articles (the reasons for exclusion are listed in Figure 1). Thus, altogether 81 articles were retained for analysis, with 53 chronic-pain studies, 24 experimental-pain studies and 4 studies investigating both experimental and chronic pain. The average quality score, based on the risk of bias criteria, was 5.5 (out of 6 or 7, depending on the design) for the chronic-pain studies and 4.4 (out of 5) for the experimental-pain studies (see Tables S1 and S2 in the supplemental material for the risk of bias data of each study). Thus, we are confident that the reported outcomes are not biased by a lack of quality of the included studies.

Table 1 and Table 2 summarize the number of significant findings for chronic pain and experimental pain, respectively. In Table 3 and Table 4, the findings of each study are presented in detail. In addition, Figure 2 displays

the average effect sizes extracted from the studies. The results are discussed below separately for the chronic-pain studies and the experimental-pain studies and organized in terms of the three executive function domains proposed by Miyake and colleagues (2000).

Chronic-Pain Studies

Fifty-seven studies investigating the association between executive functioning and chronic pain were included in this review (see Table 3). The most commonly studied chronic pain condition was fibromyalgia, which was investigated in 21 studies. Other common studied pain conditions were migraine/headache (10 studies), rheumatoid arthritis/arthrosis (7 studies), and chronic back pain (5 studies). Less commonly studied conditions include eosinophilia-myalgia, chronic pancreatitis, complex regional pain syndrome, temporomandibular disorder and chronic neuropathic/radicular pain. Sixteen studies did not investigate a specific pain condition but studied a group of patients under the name “various chronic pain conditions,” “musculoskeletal pain,” or “multiple functional somatic symptoms.”

Table 1. Percentage of tests that show a significant association between chronic pain and executive functioning

	Correlational approach Chronic pain is negatively correlated with executive functioning performance	Group comparison Chronic pain patients show reduced executive task performance compared to controls	Total
Inhibition	16.7% (3 out of 18 tests)	41.5% (17 out of 41 tests)	33.9% (20 out of 59 tests)
Updating	19.4% (6 out of 31 tests)	33.3% (18 out of 54 tests)	28.2% (24 out of 85 tests)
Shifting	21.7% (5 out of 23 tests)	32.4% (12 out of 37 test)	28.3% (17 out of 60 tests)
Total	19.4% (14 out of 72 tests)	33.3% (44 out of 132 tests)	

Table 2. Percentage of tests showing a significant association between experimental pain responses and executive functioning

	Correlational approach Executive functioning performance is negatively correlated with pain responsiveness	Interference design Executive task demand reduces pain responsiveness (executive functioning → pain)	Interference design Pain reduces executive functioning performance (pain → executive functioning)	Total
Inhibition	33.3% (16 out of 48 tests)	50.0% (3 out of 6 tests)	0% (0 out of 3 tests)	33.3% (19 out of 57 tests)
Updating	4.44% (2 out of 45 tests)	100% (3 out of 3 tests)	50% (4 out of 8 tests)	17.5% (10 out of 57 tests)
Shifting	15.4% (2 out of 13 tests)	–	66.7% (2 out of 3 test)	25.0% (4 out of 16 tests)
Total	19.6% (21 out of 107 tests)	66.7% (6 out of 9 tests)	42.9% (6 out of 14 tests)	

Table 3. Summary of papers investigating the association between chronic pain and executive functioning.

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Rheumatoid arthritis patients, 54 years, N=157	Self-report (0–100 VAS): 36.4	11.5 years	Stroop, Letter Number Sequencing	Inhibition, updating	Correlation	Stroop/Letter Number Sequencing & pain intensity: $p < 0.05$ ($\Delta = 0.17/0.24$)	Abeare et al. (2010)
Rheumatoid arthritis patients, 37.3 years, N=28; pain-free individuals, 33.7 years, N=30		7.3 years	Stroop	Inhibition	Group comparison	Stroop performance patients < controls: $p < 0.05$	Akdoğan et al. (2013)
Fibromyalgia patients, 36.2 years, N=40; same control group	Self-report (0–10 VAS): 8	3.1 years			Group comparison, correlation	Stroop performance patients < controls: $p < 0.05$ Stroop & pain intensity: ns	

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Chronic back pain patients, 21–71 years, N=6; pain-free individuals, 25–64 years, N=10		8.6 years	Stroop, Digit Span Backward, WCST	Inhibition, updating, shifting	Group comparison	Stroop/Digit Span Backward/WCST performance patients < controls: ns ($\Delta=1/0.5/-0.3$)	Apkarian et al. (2004)
Eosinophilia-myalgia patients, 46.7 years, N=23; pain-free individuals, 47.6 years, N=18			PASAT, WCST	Updating, shifting	Group comparison, correlation	PASAT/WCST performance patients < controls: $p<0.05$ ($\Delta=1.57$) WCST/PASAT & pain intensity: ns	Armstrong et al. (1997)
Frequent headache patients, 30.4 years, N=59	Self-report (0–100 VAS): 52.8 during headache		Flanker test, N-back, Cued Task Switching	Inhibition, Updating, shifting	Group comparison	Cued Task Switching performance during headache < during no headache: $p<0.05$ ($\Delta=0.4$) Flanker/N-back task performance during headache < during no headache: ns (only women: $p<0.05$)	Attridge et al. (2017)
Patients with chronic low back pain, 74.5 years, N=8; pain-free individuals, 69.9 years, N=8	MPQ-SF: 30.75	>3 months	Digit Span Backward, Letter Number Sequencing, TMT (B)	Updating, shifting	Group comparison	Digit Span Backward/Letter Number Sequencing/TMT (B) performance patients < controls: ns ($\Delta=1/0.5/0.91$)	Buckalew et al. (2008)
Fibromyalgia patients, 63.0 years, N=43; pain-free individuals, 64.8 years, N=44	Self-report: 6.3 (0–10 VAS)		Stroop, Digit Span Backward, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting	Group comparison	Stroop performance patients < controls: $p<0.05$ ($\Delta=0.51$) Digit Span Backward/Verbal Fluency task TMT (B) performance patients < controls: ns ($\Delta=0.45/-0.23/0.13$)	Cherry et al. (2014)
Fibromyalgia patients, 44.5 years, N=21; Pain-free individuals, 38.0 years, N=22		96.3 months	Stroop, OSPAN	Inhibition, updating	Group comparison	Stroop/OSPAN performance patients < controls: $p<0.05$	Coppieters et al. (2015)
Fibromyalgia patients, 48.0 years, N=18; pain-free individuals, 42.0 years, N=19	MPQ: 7.61	4 years	Go-/No-go task	Inhibition	Group comparison	Go-/No-go task performance patients < controls: $p<0.05$ ($\Delta=0.29$)	Correa et al. (2011)

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Fibromyalgia patients, 41.29 years, N=40; Pain-free individuals, 40.72 years, N=41	FIQ: 7 (0–10 NRS)	6.47 years	Tower of London, Digit-Span Backward, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting	Group comparison	Tower of London/Digit-Span Backward/Verbal Fluency task/TMT (B) performance patients < controls: $p < 0.05$ ($\Delta = 0.56/0.88/0.80/n/a$)	Di Tella et al. (2015)
Fibromyalgia patients, 48.0 years, N=20; Pain-free individuals, 60.0 years, N=20	Self-report: 4.6 (0–10 VAS)	11.0 years	Test of Everyday Attention: updating and shifting	Updating, shifting	Group comparison, correlation	Updating performance patients < controls: $p < 0.05$ ($\Delta = 0.98$) Shifting performance patients < controls: ns ($\Delta = 0.10$) Updating/shifting & pain intensity: ns	Dick et al. (2002)
Rheumatoid arthritis patients, 62.9 years, N=20; same control group	Self-report: 4.5 (0–10 VAS)	18.9 years				Updating performance patients < controls: $p < 0.05$ ($\Delta = 1.64$) Shifting performance patients < controls: ns ($\Delta = 0.68$) Updating/shifting & pain intensity: ns	
Musculoskeletal disorder patients, 52.3 years, N=20; same control group	Self-report: 4.7 (0–10 VAS)	10.2 years				Updating/shifting performance patients < controls: ns ($\Delta = 0.84/0.61$) Updating/shifting & pain intensity: ns	
Patients with migraine and obesity, 38.3 years, N=124	Self-report: 5.9 (0–10)		Stroop	Inhibition	Correlation	Stroop/Flanker test performance & pain intensity: ns (interictal assessment)	Galioto et al. (2018)
Patients with various chronic pain conditions, 51.9 years, N=1399			Stroop	Inhibition	Correlation	Stroop performance & pain intensity: $p < 0.05$ ($\Delta = 0.12$)	Gijssen et al. (2011)
Migraine patients, 38.0 years, N=24	Self-report: 5.7 (0–10 VAS) during migraine attack	19.30 years	Stroop, Digit Span Backward, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting	Group comparison	Stroop/Digit Span Backward/Verbal Fluency task/TMT (B) performance during attack < during no headache: ns ($\Delta = 0.19/0.35/0.35/0.11$)	Gil-Gouveia et al. (2015)

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Fibromyalgia patients, 43.6 years, N=18; pain-free individuals, 41.1 years, N=14	PED: 55.4 (0–100)		Go-/No-Go Task	Inhibition	Group comparison, correlation	Go-/No-Go Task performance patients < controls: ns ($\Delta=0.11$) Go-/No-Go Task performance & pain intensity: ns	Glass et al. (2011)
Fibromyalgia patients, 48.9 years, N=32; pain-free individuals, 48.4 years, N=30	Self-report: 6.5 (0–10 VAS)		N-back	Updating	Group comparison	N-back task performance patients < controls: ns ($\Delta=0.20$)	González-Villar et al. (2017)
Fibromyalgia patients, 45.9 years, N=29 (+7 for correlation analysis); pain-free individuals, 44.7 years, N=29	Self-report: 4.2 (0–10 VAS)		PASAT	Updating	Group comparison, correlation	PASAT performance patients < controls: $p<0.05$ ($\Delta=0.61$) PASAT performance & pain intensity: $p<0.05$ ($r=0.36$)	Grace et al. (1999)
Patients with various chronic pain conditions, 45.0 years, N=33; pain-free individuals, 45.0 years, N=20	Low-pain patients: 31.0 (0–100 VAS) High-pain patients: 73.0	>1 year	Modified Stroop: inhibition and shifting	Inhibition, shifting	Group comparison	Inhibition/shifting performance high-pain patients < controls: $p<0.05$	Grisart & Plaghki (1999)
Multiple functional somatic symptoms patients, 36.6 years, N=22; pain-free individuals, 35.6 years, N=27	Self-report: 2.63 (0–10 VAS)	10.5 years	Digit Span Backward, COWAT, TMT (B)	Updating, shifting	Group comparison, correlation	Digit Span Backward/COWAT/TMT (B) performance patients < controls: $p<0.05$ ($\Delta=0.69/0.74/0.85$) Digit Span Backward/TMT (B) performance & pain intensity: $p<0.05$ ($r=0.71/0.49$) COWAT performance & pain intensity: ns ($r=0.34$)	Hall et al. (2011)
Fibromyalgia with comorbid chronic fatigue syndrome patients, 40.2 year, N=30; pain-free individuals, 37.3 years, N=30	Self-report: 39.9 (0–100 SF-36)	11.3 years	Stroop, OSPAN	Inhibition, updating	Group comparison, correlation	Stroop performance patients < controls: $p<0.05$ ($\Delta=1.41$) OSPAN performance patients < controls: ns ($\Delta=0.44$) Stroop/OSPAN & pain intensity: ns	Ickmans et al. (2015)
Chronic pancreatitis patients, 49.5 years, N=16; pain-free individuals, 48.0 years, N=16		6.1 years	Verbal Interference, Go-/No-Go Task, Switching of Attention test	Inhibition, shifting	Group comparison	Go-/No-Go Task/Verbal Interference Switching of Attention test performance patients < controls: $p<0.05$ ($\Delta=0.72/0.94/0.68$)	Jongsma et al. (2011)

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Fibromyalgia patients, 42.2 years, N=50	Self-report: 5.8 (0–10 VAS)		Domain executive functioning: Go-/No-Go Task, Stroop	Inhibition	Group comparison (to normative data), correlation	Stroop/Go-/No-Go Task performance patients < controls: ns Executive functioning domain performance & pain intensity: $p < 0.05$ ($r = 0.32$)	Kalfon et al. (2016)
Patients with various chronic pain conditions, 76.1 years, N = 56	Self-report: 58.1 (0–100 VAS)		TMT (B)	Shifting	Correlation	TMT (B) performance & pain intensity: $p < 0.05$ ($r = 0.42$)	Karp et al. (2006)
Migraine patients, 38.8 years, N=24; pain-free individuals, 43.1 years, N=24			Stroop	Inhibition	Group comparison	Stroop performance patients < controls: ns ($\Delta = 0.11$)	Kröner-Herwig et al. (2005)
Tension-type headache patients, 42.8 years, N=18; same control group						Stroop performance patients < controls: ns ($\Delta = 0.41$)	
Chronic low back pain patients, 45.0 years, N=12; pain-free individuals, 44.0 years, N=14	Self-report: 25–48 (0–100 VAS)	7–15 years	Stroop	Inhibition	Group comparison	Stroop performance patients < controls: $p < 0.05$	Lamoth et al. (2008)
Complex regional pain syndrome patients, 36.1 years, N=25; pain-free individuals, 31.7 years, N=25		2.8 years	Stop-signal task, WCST	Inhibition, shifting	Group comparison	Stop-signal task/WCST performance patients < controls: $p < 0.05$ ($\Delta = 1.36/0.97$)	Lee et al. (2015)
Patients with various chronic pain conditions, 37.7 years, N = 38	MPQ: 21.4	10.7 years	Stroop, COWAT, TMT (B)	Inhibition, updating, shifting	Correlation	Stroop/COWAT/TMT (B) performance & pain intensity: ns ($r = 0.02/0.10/0.02$)	Legaretta et al. (2016)
Fibromyalgia patients, 53.6 years, N = 20	MPQ: 63.5	14.4 years	Digit Span Backward, Corsi Block Span, TMT (B)	Updating, shifting	Group comparison (to normative data), correlation	Corsi Block Span performance patients < controls: $p < 0.05$ Digit Span Backward/TMT (B) performance patients < controls: ns Digit Span Backward/Corsi Block Span/TMT (B) & pain intensity: ns	Luerding et al. (2008)

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Migraine patients, 61.9 years, N=61; pain-free individuals, 66.8 years, N=367			Stroop, Digit Span Backward, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting	Group comparison	Stroop/Digit Span Backward/Verbal Fluency task/TMT (B) performance patients < controls: ns (Interictal assessment)	Martins et al. (2012)
Non migraine headache patients, 69.3 years, N=50; same control group						Stroop/Digit Span Backward/Verbal Fluency task/TMT (B) performance patients < controls: ns	
Fibromyalgia patients, 49.8 years, N=29; pain-free individuals, 46.3 years, N=31	Self-report: 45.3 (0–100 VAS)	8.9 years	Stroop	Inhibition	Group comparison	Stroop performance patients < controls: p<0.05 ($\Delta=0.89$)	Martinsen et al. (2014)
Chronic lower back pain patients, 59.6 years, N=29; pain-free individuals, 60.7 years, N=30	Self-report: 56 (0–100 VAS)	7.58 years	Stroop, TMT (B)	Inhibition, shifting	Group comparison, correlation	Stroop/TMT (B) performance patients < controls: ns ($\Delta=0.07/0.29$) Stroop/TMT (B) & pain intensity: ns	Masiūnas et al. (2017)
Fibromyalgia patients, 46.6 years, N=33; pain-free individuals, 42.9 years, N=28	MPQ: 20.92	4.27 years	ANT-I (attentional network test-interactions)	Inhibition	Group comparison, correlation	ANT-I performance patients < controls: p<0.05 ($\Delta=0.79$) ANT-I performance & pain intensity: ns (r=0.03)	Miró et al. (2011)
Fibromyalgia patients, 45.9 years, N=77; pain-free individuals, 44.7 years, N=48			ANT-I (attentional network test-interactions)	Inhibition	Group comparison, correlation	ANT-I performance patients < controls: p<0.05 ANT-I performance & pain intensity: ns	Miró et al. (2015)
Headache patients, 24.9, N=75			N-back task, Attentional Switching task	Updating, shifting	Group comparison, correlation	N-back task/Attentional Switching task performance during headache < during no headache: p<0.05 ($\Delta=0.57/0.12$) N-back task/Attentional Switching task performance & pain intensity: ns	Moore et al. (2013A)

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Patients with chronic neuropathic or radicular pain, 45.6 years, N=38; pain-free individuals, 44.2 years, N=38	CPG: 73.2	8.5 years	WCST	Shifting	Group comparison, correlation	WCST performance patients < controls: ns ($\Delta=0.35$) WCST performance & pain intensity: ns	Moriarty et al. (2017)
Knee osteoarthritis patients, 70.0 years, N=79	MPQ-SF: 14.7	>3 months	Tracking test	Shifting	Correlation	Tracking test performance & pain intensity: ns	Morone et al. (2014)
Chronic musculoskeletal pain patients, 74.6 years, N=44; pain-free individuals, 72.2 years, N=190	>4 (0–10 NRS)	>3 months	Letter and Category Verbal Fluency task, TMT (B)	Updating, shifting	Group comparison	Category Verbal Fluency task performance patients < controls: $p<0.05$ ($\Delta=0.42$) Letter Verbal Fluency task/TMT (B) performance patients < controls: ns ($\Delta=-0.12/0.17$)	Murata et al. (2017)
Patients with various chronic pain conditions, 39.9 years, N=40; pain-free individuals, 35.0 years, N=29	Self-report: 6.35 (0–10 VAS)		A Quick Test, Digit Span Backward, TMT (B)	Inhibition, updating, shifting	Group comparison	A Quick Test performance patients < controls: $p<0.05$ ($\Delta=0.86$) Digit Span Backward/TMT (B) performance patients < controls: ns ($\Delta=0.47/0.86$)	Nadar et al. (2016)
Patients with various chronic pain conditions, 51.5 years, N=34; pain-free individuals, 55.4 years, N=32	Self-report: 34.9 (0–100 VAS)	11.7 years	Digit Span Backward	Updating	Group comparison, correlation	Digit Span Backward performance patients < controls: $p<0.05$ ($\Delta=0.44$) Digit Span Backward performance & pain intensity: $p<0.05$ ($r=0.38$)	Oosterman et al. (2011)
Patients with various chronic pain conditions, 51.5 years, N=34; pain-free individuals, 55.4 years, N=32	Self-report: 34.9 (0–100 VAS)	11.7 years	Stroop, Zoo Map test, TMT (B),	Inhibition, updating, shifting	Group comparison, correlation	TMT (B) performance patients < controls: $p<0.05$ ($\Delta=0.76$) Stroop/Zoo Map test performance patients < controls: ns ($\Delta=0.07/0.16$) Stroop/Zoo Map test/TMT (B) performance & pain intensity: ns	Oosterman et al. (2012)

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Patients with various chronic pain conditions, 28.8 years, N=22		9.8 years	Stroop, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting	Correlation	TMT (B) performance & pain intensity: $p < 0.1$ Stroop/Verbal Fluency task performance & pain intensity: ns	Oosterman et al. (2013)
Patients with various chronic pain conditions, 65.0 years, N=24		10.6 years				TMT (B) performance & pain intensity: $p < 0.05^*$ Stroop/Verbal Fluency task performance & pain intensity: ns	
Fibromyalgia patients, 47.83 years, N=23; pain-free individuals, 47.83 years, N=23	MPQ: 33.8		Reading and computational Span task (working memory domain), Verbal Fluency task	Updating	Group comparison, correlation	Working memory performance patients < controls: $p < 0.05$ ($\Delta = 2.44$) Verbal Fluency task performance patients < controls: ns ($\Delta = 0.40$) Working memory performance & pain intensity: $p < 0.05$ ($r = 0.61$) Verbal Fluency task performance & pain intensity: ns	Park et al. (2001)
Migraine patients without aura, 36.7 years, N=32; pain-free individuals, 35.8 years, N=16		18.4 years	Stroop, COWAT, TMT (B),	Inhibition, updating, shifting	Group comparison	COWAT performance patients < controls: $p < 0.05$ ($\Delta = 1.11$) Stroop/TMT (B) performance patients < controls: ns ($\Delta = 0.47/0.87$) (Interictal assessment)	Le Pira et al. (2014)
Migraine with aura, 42.1 years, N=12; same control group		16.3 years				Stroop/COWAT/TMT (B) performance patients < controls: ns (Interictal assessment) ($\Delta = 0.33/1.03/0.55$)	
Patients with various chronic pain conditions, 48.5 years, N=30	Self-report: 43 (0–100 VAS)	7 years	Stroop, Verbal Fluency task, TMT (B)	Inhibition, updating, shifting	Correlation	Stroop/Verbal Fluency task/TMT (B) performance & pain intensity: ns ($r = 0.08/0.12/0.21$)	Pulles & Oosterman (2011)
Fibromyalgia patients, 48.5 years, N=15; pain-free individuals, 44.3 years, N=15		1.1 years	Stroop, Digit Span Backward	Inhibition, updating	Group comparison	Stroop/Digit Span Backward performance patients < Stroop/Digit Span Backward performance controls: ns	Roldán-Tapia et al. (2007)

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Rheumatoid arthritis patients, 41.9 years, N=15; same control group		1.6 years				Stroop/Digit Span Backward performance patients < Stroop/Digit Span Backward performance controls: ns	
Patients with arthrosis/arthriti- tis, 85.7 years, N=20	Self-report: 50.85 (0–100 CAS)		Executive functioning domain: Digit Span Back- ward, Category Fluency, Knox's Cube Imitation Test, Incom- plete figures	Updating	Correlation	Executive func- tioning perfor- mance & pain intensity: ns ($r=0.17$)	Scherder et al. (2008)
Patients with arthrosis/arthriti- s and Alzheimer's disease, 86.4 years, N=19	Self-report: 21.55 (0–100 CAS), 0.56 (0–6 FPS)					Executive func- tioning perfor- mance & pain intensity: $p<0.05^*$ ($r=-0.675$)	
Patients with vari- ous chronic pain conditions, 44.4 years, N=91; pain- free individuals, 47.6 years, N=64		7 years	PASAT	Updating	Group comparison, correlation	PASAT perfor- mance patients < controls: ns ($\Delta=0.20$) PASAT perfor- mance & pain intensity: $p<0.05$	Sjögren et al. (2005)
Fibromyalgia pa- tients, 48.1 years, N=23; pain-free individuals, 45.9 years, N=21	MPQ: 38.0		Stroop, Letter Number Sequencing, COWAT, PASAT, TMT (B), WCST	Inhibition, updating, shifting	Group comparison, correlation	Stroop/Letter Num- ber /COWAT/PASAT/ WCST/TMT (B) per- formance patients < controls: ns ($\Delta=0.51/0.70/0.33/0.62/-0.03/1.48$) Stroop/WCST/ Let- ter Number /COW- AT/PASAT/TMT (B) performance & pain intensity: ns	Suhr (2003)
Patients with vari- ous chronic pain conditions, 49.5 years, N=22; same control group	MPQ: 20.9					Stroop/Letter Num- ber /COWAT/PASAT/ WCST/TMT (B) per- formance patients < controls: ns ($\Delta=-$ $0.02/0.67/0.25/0.20/0.49/1.76$) Stroop/WCST/ Let- ter Number /COW- AT/PASAT/TMT (B) performance & pain intensity: ns	
Chronic musculo- skeletal pain patients, 57.9 years, N=15; pain- free individuals, 25–83 years, N=14	Self-report median: 60 (0–100 NRS)		Emotional counting Stroop	Inhibition	Group comparison	Stroop perfor- mance patients < Stroop perfor- mance controls: $p<0.05$	Taylor et al. (2016)

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Patients with migraine with aura, 30.1 years, N=20; pain-free individuals, 29.2 years, N=20	Attack self-report: 8.0 (0–10 VAS)	11.0 years	Verbal Fluency task, TMT (B), WCST	Updating, shifting	Group comparison	Verbal Fluency task/TMT (B)/WCST performance patients < controls: ns ($\Delta=0.87/0.60/0.14$) (Interictal assessment)	Tessitore et al. (2015)
Patients with migraine without aura, 30.1 years, N=20; same control group	Attack self-report: 8.6 (0–10 VAS)	11.2 years				Verbal Fluency task/TMT (B)/WCST performance patients < controls: ns ($\Delta=0.38/0.68/-0.14$) (Interictal assessment)	
Episodic cluster headache patients, 40.8 years, N=11; pain-free individuals, 53.2 years, N=12		10.8 years	Stroop, Verbal Fluency task, Digit Span, Letter-number Sequencing, TMT (B)	Inhibition, Updating, shifting	Group comparison	Digit Span/TMT (B) performance patients < controls: $p<0.05$ ($\Delta=1.65/2.44$) Stroop/Letter-number Sequencing Verbal Fluency task performance patients < controls: ns ($\Delta=1.10/1.31/0.47$) (Assessment during headache episode)	Torkamani et al. (2015)
Chronic cluster headache patients, 49.2 years, N=11; same control group		14.6 years				Digit Span/Letter-number Sequencing performance patients < controls: $p<0.05$ ($\Delta=1.63/1.39$) Stroop/Verbal Fluency task/TMT (B) performance patients < controls: ns ($\Delta=1.34/1.21/1.71$) (Interictal assessment)	
Elderly with various chronic pain conditions, 78.1 years, N=765			Clock-in-the-box Test, Letter Fluency task, TMT (B)	Updating, shifting	Correlation	Clock-in-the-box Test/Letter Fluency task/TMT (B) performance & pain intensity: ns	van der Leeuw et al. (2016)
Fibromyalgia patients, 30.4 years, N=35; Pain-free individuals, 29.3 years, N=35	Self-report: 49 (0–100 VAS)		Stroop, Multi-source Interference Test	Inhibition	Group comparison	Stroop/Multi-source Interference Test performance patients < controls: ns ($\Delta=0.51/-0.15$)	Veldhuijzen et al. (2012)

Table 3. continuation

Participants	Pain intensity patients	Disease duration	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Fibromyalgia patients, 45.9 years, N=36; pain-free individuals, 45.0 years, N=36	WHYMPI: 4.62 (0–6 NRS)	11.5 years	WCST	Shifting	Group comparison, correlation	WCST performance patients < controls: $p < 0.05$ ($\Delta = 0.75$) WCST performance & pain intensity: $p < 0.05$ ($r = 0.23$)	Verdejo-García et al. (2009)
Fibromyalgia patients, 50.4 years, N=15; pain-free individuals, 49.0 years, N=15	Self-report: 4.5 (0–10 VAS)	>6 months	Stroop, Digit Span	Inhibition, updating	Group comparison	Stroop/Digit Span performance patients < controls: ns ($\Delta = 0.64/0.09$)	Walteros et al. (2011)
Chronic low back pain patients, 73.6 years, N=163; pain-free individuals, 73.5 years, N=160	MPQ: 12.2	14.2 years	TMT (B)	Shifting	Group comparison, correlation	TMT (B) performance patients < controls: $p < 0.05$ ($\Delta = 0.25$) TMT (B) performance & pain intensity: $p < 0.05$	Weiner et al. (2006)
Temporomandibular disorder patients, 35.2 years, N=17; pain-free individuals, 34.0 years, N=17	Self-report: 4.2 (0–10 NRS)	9.3 years	Counting Stroop	Inhibition	Group comparison	Stroop performance patients < controls: ns ($\Delta = 0.63$)	Weissman-Fogel et al. (2011)

*Positive association

Abbreviations: VAS = Visual Analogue Scale; WCST = Wisconsin Card Sorting Test; PASAT = Paced Auditory Serial Addition Test; TMT = Trail Making Test; OSPAN = Operation Span Task; FIQ = Fibromyalgia Impact Questionnaire; CPG = Chronic Pain Grade; PED = Patient Experience Diary; NRS = Numerical Rating Scale; COWAT = Controlled Oral Word Association Test; MPI = Multidimensional Pain Inventory; WAIS-R = Wechsler Adult Intelligence Scale Revised; MPQ(-SF) = McGill Pain Questionnaire (Short Form); SF-36 = Short Form (36) health survey (higher scores represent less pain); CAS = Colored Analogue Scale; FPS = Faces Pain Scale; WHYMPI = West Haven-Yale Multidimensional Pain Inventory; n/a = not available; r = correlation coefficient, Δ = Glass' Δ effect size, ns = nonsignificant.

Most studies (46 studies) compared executive functioning performance between chronic-pain patients and pain-free individuals (group-comparison design). Thirty studies correlated self-reported pain intensity of chronic-pain patients with executive functioning performance (correlational approach). Three studies assessed executive functioning performance with and without headache attack (Attridge et al., 2017; Gil-Gouveia et al., 2015; Moore et al., 2013A). We decided to label these three studies as group comparison designs, given that they follow a similar logic.

Inhibition – Chronic-Pain Studies

The most commonly used task to measure inhibition was the Stroop task (29 studies). In total, 33.9% of all 59 tests confirmed that there is a significant association between inhibition and chronic pain (Table 1). Most of these tests were group comparisons, 41.5% of which showed that the ability to inhibit is significantly reduced in chronic-pain

patients compared to pain-free individuals. In line with this, the computation of effect sizes for the group comparisons revealed medium effects. Interestingly, this reduced ability to inhibit (on a group-level) does not seem to be closely linked to the intensity of the chronic pain (correlational approach), given that only a small percentage of tests (16.7%) showed that a high pain intensity is significantly correlated with reduced inhibition performance. These meager results were also reflected in a very small averaged effect size (correlation coefficients, see Figure 2).

Updating – Chronic-Pain Studies

The most commonly used task to measure information updating and monitoring was the digit span backwards task (15 studies). Other commonly reported tasks included verbal fluency tasks, the Operation Span Task, and the Paced Auditory Serial Addition Test (see Table 3). In total,

Table 4. Summary of papers investigating the association between experimental pain and executive functioning.

Sample	Pain stimulus	Pain measure	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Pain-free individuals, 30.0 years, N=8	Heat	Intensity	Stroop	Inhibition	Interference	Pain intensity during Stroop interference < during Stroop neutral: $p < 0.05$	Bantick et al. (2012)
Pain-free individuals, 26.0 years, N=16	Infrared laser	Intensity	N-back	Updating	Interference	Pain intensity during 2-back task < during 1-back task: $p < 0.05$ 2-Back task performance during pain < during no pain: $p < 0.05$	Bingel et al. (2007)
Pain-free individuals, 22.6 years, N=54	Cold pressor test	Threshold and tolerance	Stroop, Stop-signal, Left-right, Keep-track, Letter-memory, N-back, Plus-minus, Number-letter, Local-global	Inhibition, updating, shifting	Correlation	Stroop & threshold/tolerance: $p < 0.05$ ($r = 0.28/0.40$) Stop-signal/Left-right/Keep-track/Letter-memory/N-back/Plus-minus/Number-letter/Local-global & threshold: ns ($r = -0.10/0.03-0.13/0.04/0.01/0.016/-0.01$) Stop-signal/Left-right/Keep-track/Letter-memory/N-back/Plus-minus/Number-letter/Local-global & tolerance: ns ($r = -0.16/0.08/-0.01/-0.02/-0.01/-0.06/-0.04$)	Bjekić et al. (2017)
Pain-free individuals, 21.5 years, N=61	Heat		Task-shifting	Shifting	Interference	Task-shifting performance during pain < during no pain: $p < 0.05$	Boselie et al. (2017)
Pain-free individuals, 25.0 years, N = 24	Heat	Intensity	N-Back task	Updating	Interference	Pain intensity during 3-back task < during neutral task: $p < 0.05$ 3-back task performance during pain < 3-back task performance during no pain: $p < 0.05$	Buhle and Wager (2010)
Pain-free individuals, 26.0 years, N=12	Esophageal pressure	Intensity	N-back task	Updating	Interference	Pain intensity during 1-back task < during neutral task: $p < 0.05$ 1-Back task performance during pain < during no pain: ns	Coen et al. (2008)
Pain-free individuals, 38.0 years, N=22	Pressure	Threshold cuff, CPM finger and shoulder, TS finger and shoulder	Stroop, OSPAN	Inhibition, updating	Correlation	Stroop & CPM shoulder: $p < 0.05$ ($r = 0.45$) Stroop & threshold cuff/CPM finger/TS finger/TS shoulder: ns ($r = -0.01/0.30/0.33/0.08$)	Coppieters et al. (2015)

Table 4. continuation

Sample	Pain stimulus	Pain measure	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
						OSPAN & threshold cuff/CPM finger/CPM shoulder/TS finger/TS shoulder: ns (r=0.31/0.29/0.18/0.09/-0.16)	
Fibromyalgia patients, 44.5 years, N=21						OSPAN & TS shoulder: p<0.05 (r=0.53) OSPAN & threshold cuff/CPM finger/CPM shoulder/TS finger: ns (r=0.19/-0.07/-0.19/0.43) Stroop & threshold cuff/CPM finger/CPM shoulder/TS finger/TS shoulder: ns (r=-0.09/-0.17/0.33/0.30/0.17)	
Pain-free individuals, 37.3 years, N=30	Pressure	Threshold, CPM, TS; all on finger and shoulder	Stroop, OSPAN	Inhibition, updating	Correlation	Stroop/OSPAN & threshold finger/threshold shoulder/CPM finger/CPM shoulder/TS finger/TS shoulder: ns	Ickmans et al. (2015)
Chronic fatigue syndrome with comorbid fibromyalgia patients, 40.2 year, N=30						Stroop/OSPAN & CPM finger: p<0.05 (r=0.41/0.55) Stroop/OSPAN & threshold finger/threshold shoulder/CPM shoulder/TS finger/TS shoulder: ns	
Pain-free individuals, 22.2 year, N=49	Heat	Intensity measured by facial expression	Stroop, anti-saccade task	Inhibition	Correlation	Anti-saccade & facial expression: p<0.05 (r=0.31) Stroop & facial expression: ns (r=-0.17)	Karmann et al. (2015)
Pain-free individuals, 21.8 year, N=57	Cold pressor test	Tolerance	Stop-signal	Inhibition	Correlation	Stop-signal & tolerance: p<0.05	Karsdorp et al. (2014)
Pain-free individuals, 20.6 years, N=70	Finger-pressing task	Tolerance	Stop-signal	Inhibition	Correlation	Stop-signal & tolerance: p<0.05	Karsdorp et al. 2016
Pain-free individuals, 25.0 years, N=62	Heat		Word Generation task	Updating	Interference	Word generation task performance during pain < during no pain: ns	Keogh et al. (2013)
Pain-free individuals (dementia, mild cognitive impairments, 75.6 years, N=70)	Electrical stimuli	Nociceptive flexion reflex threshold and facial expression	SIDAM (domain intellectual abilities/executive function)	Shifting	Correlation	SIDAM & nociceptive flexion reflex threshold/facial expression: p<0.05	Kunz et al. (2015)

Table 4. continuation

Sample	Pain stimulus	Pain measure	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Pain-free individuals, 30.0 years, N=10	Infrared laser		N-back	Updating	Interference	Performance 1-back task during pain < during no pain: ns	Legrain et al. (2011)
Pain-free individuals, 25.0 year, N=16	Infrared laser		N-back	Updating	Interference	Performance 1-back task during pain < during no pain: ns	Legrain et al. (2013)
Pain-free individuals, ~45.9 years, N=44	Electrical stimulation	CPM	Stroop	Inhibition	Correlation	Stroop & CPM: $p < 0.05$ ($r = 0.34$)	Marouf et al. (2014)
Pain-free women, 46.3 years, N=31	Pressure	Threshold	Stroop	Inhibition	Interference	Threshold during Stroop interference > during control condition: ns	Martinsen et al. (2014)
Fibromyalgia patients, 49.8 years, N=29						Threshold during Stroop interference > during control condition: ns	
Pain-free individuals, 40.9 years, N=16	Pressure	Threshold, CPM; both on finger and shoulder	Stroop, OSPAN	Inhibition, updating	Correlation	Stroop & CPM finger/CPM shoulder: $p < 0.05$ ($r = 0.61/0.60$) Stroop & threshold finger/threshold shoulder: ns ($r = -0.26/-0.29$) OSPAN & CPM finger/CPM shoulder/threshold finger/threshold shoulder: ns ($r = -0.33/-0.32/-0.4/0.03$)	Meeus et al. (2015)
Pain-free individuals, 22.06 years, N=50	Heat		N-back task, Attentional Switching task	Updating, shifting	Interference	N-back/Attentional switching performance during pain < during no pain: $p < 0.05$	Moore et al. (2013B)
Pain-free individuals, 30.0 years, N=20	Heat		N-back task	Updating	Interference	N-back performance during pain < during no pain: $p < 0.05$	Moore et al. (2017)
Pain-free individuals, 31.0 years, N=20			Attentional Switching task	Shifting		Attentional switching performance during pain < during no pain: ns	
Pain-free individuals, 59.1 years, N=31	Cold pressor test	Tolerance, intensity	Stroop, Letter fluency test, Digit Span Backward, Zoo Map Test, TMT (B)	Inhibition, updating, shifting	Correlation	Stroop & tolerance: $p < 0.05$ ($r = 0.42$) Letter fluency test/TMT (B)/Zoo Map Test/Digit Span Backward & tolerance: ns ($r = 0.04/-0.29/-0.26/-0.35$) Stroop/Letter fluency test/TMT (B)/Zoo Map Test/Digit Span Backward & pain intensity: ns ($r = 0.33/0.08/-0.04/-0.29/-0.11$)	Oosterman et al. (2010)

Table 4. continuation

Sample	Pain stimulus	Pain measure	Executive functioning tests	Cognitive domain	Study design	Significance of findings and effect sizes	Reference
Pain-free individuals, 66.7 years, N=51	Pressure	Intensity measured by rating and facial expression	Stroop, Digit Span Backward, Zoo Map Test	Inhibition, updating	Correlation	Stroop & pain intensity/facial expression: $p < 0.05$ Digit Span Backward/Zoo Map Test & pain intensity/facial expression: ns	Oosterman et al. (2016)
Pain-free individuals, 26.4 years, N=16	Electrical nerve stimulation		Counting Stroop	Inhibition	Interference	Counting Stroop performance during pain < during no pain: ns	Seminowicz et al. (2004)
Pain-free individuals, 25.6 years, N=23	Electrical nerve stimulation	Intensity	Multisource interference task	Inhibition	Interference	Pain intensity during multisource interference test difficult < during multisource easy: ns Multisource interference test performance during pain < during pain: ns	Seminowicz and Davis (2007)
Pain-free individuals, 24.0 years, N=36	Cold pressor test	Tolerance	Stroop	Inhibition	Interference	Stroop performance during pain < during no pain: ns Pain tolerance during Stroop > during Stroop neutral: $p < 0.05$	Terrighena et al. (2017)
Pain-free individuals, 32.1 years, N=7	Heat	Intensity	Stroop	Inhibition	Interference	Pain intensity during Stroop task < during Stroop neutral: $p < 0.05$	Valet et al. (2004)
Pain-free women, 29.3 years, N=35	Pressure	Threshold	Stroop, Multisource Interference Test	Inhibition	Correlation	Stroop/multisource interference test & threshold: ns ($r = 0.2/0.34$)	Veldhuijzen et al. (2012)
Fibromyalgia patients, 30.4 years, N=35						Stroop/multisource interference test & threshold: $p < 0.05$ ($r = 0.41/0.37$)	
Pain-free individuals, 67.5 years, N=26	Cold pressor test	Threshold, tolerance, intensity	Stroop, Letter Fluency test, TMT (B)	Inhibition, updating, shifting	Correlation	Stroop & pain intensity: $p < 0.05$ ($r = 0.48$) Stroop & threshold/tolerance: ns ($r = -0.2/-0.2$) TMT (B) & threshold/tolerance/pain intensity: ns ($r = 0.09/0.09/-0.1$) Letter Fluency test & threshold/tolerance/pain intensity: ns ($r = 0.26/0.26/-0.31$)	Zhou et al. (2015)

Abbreviations. CPM=Conditioned Pain Modulation; TS=Temporal Summation; OSPAN=Operation Span Task; SIDAM=Structured Interview for the Diagnosis of dementias of the Alzheimer type and Multi-infarct dementia and dementias of other aetiology; TMT=Trail Making Test; r =correlation coefficient, Δ =Glass' Δ effect size.

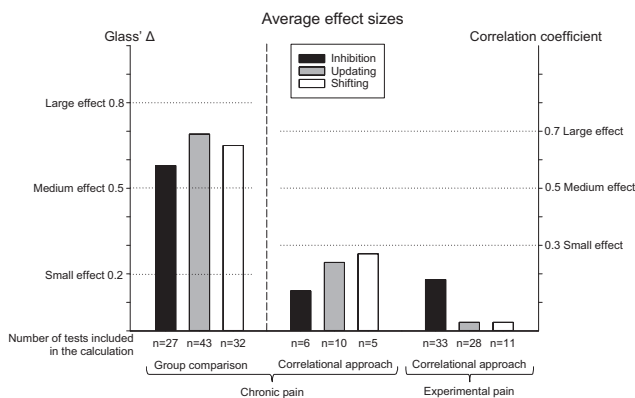


Figure 2. Average effect sizes for the association between pain (chronic and experimental pain) and the three executive functioning domains (inhibition, shifting, and updating). Glass' Δ effect size was computed for group differences (chronic-pain patients vs. controls). The correlation coefficient indicates the strength of association between executive functioning performance and pain (intensity in chronic pain or responsiveness to experimental pain, respectively). The number of tests included in the calculation are shown in the figure because effect sizes were not available for every study. The effect sizes of the experimental-pain studies using interference designs could not be calculated, given the lack of descriptive data reported in the original studies. The interpretation of the strength of the effect sizes is based on Cohen (1988) and Mukaka et al. (2012).

28.2% of all 85 tests confirmed that there is a significant association between updating and pain (Table 1). Again, stronger findings were found for group comparisons. One-third of these studies showed that updating performance is significantly reduced in chronic-pain patients compared to pain-free individuals. In line with this, there was a medium-to-large effect size for group differences between patients and controls. The correlations between pain intensity and updating performance show that only 19.4% of the tests demonstrated that higher pain intensity in patients is significantly correlated with reduced updating performance. Only one study (3.2% of all tests using a correlational approach) reported a significant correlation in the opposite direction, namely, within a group of Alzheimer patients with arthrosis or arthritis (Scherder et al., 2008). The averaged correlation coefficients point to very small effects (see Figure 2).

Shifting – Chronic-Pain Studies

The Trail Making Test B was used most often to assess shifting performance (23 studies). The Wisconsin Card Sorting task was also used frequently (see Table 3). In total, 28.3% of all 60 tests confirmed that there is a significant association between pain and shifting performance (Table 1). Similar to updating, almost one-third of the group comparisons showed that shifting ability is significantly reduced in chronic-pain patients, which is also re-

flected in moderate-to-large effect sizes (see Figure 2). A smaller proportion (21.7%) found that reduced shifting performance is significantly correlated to a higher pain intensity in patients. One study (4.3% of all tests using a correlational approach) found that higher pain intensity was correlated with better shifting performance, namely, in a group of elderly with various chronic pain conditions (Oosterman et al., 2013). On average, correlation coefficients point to a very small association between pain intensity and shifting performance (see Figure 2).

Summary – Chronic-Pain Studies

There is medium to strong evidence that executive functioning performance is reduced in chronic-pain patients compared to pain-free controls, with all three domains of executive functioning being similarly affected. In contrast, the evidence for a significant correlation between the intensity of chronic pain and executive functioning performance is much weaker.

Experimental-Pain Studies

Twenty-eight studies investigated the association between executive functioning and experimental pain responses (see Table 4). The most commonly used methods of inducing pain were thermal heat pain and pressure pain, both used in eight studies. Other methods were the cold pressor test, electrical stimulation, and infrared laser stimulation.

Thirteen studies investigated whether responsiveness to painful stimulation is correlated with executive functioning performance (correlational approach). Twelve studies investigated whether painful stimulation reduces executive functioning performance (pain → executive functioning) by letting the participants perform an executive task twice, once while receiving painful stimulation and once without receiving painful stimulation (6 studies) or with nonpainful stimulation (6 studies). In seven studies participants received painful stimulation twice, once while performing an executive function task and once while performing a neutral task, to investigate whether executive task demand reduces responsiveness to painful stimulation (executive functioning → pain).

Inhibition – Experimental-Pain Studies

Similar to the chronic-pain studies, the most commonly used task to measure inhibition was the Stroop task (15 studies). In total, one-third of the 57 tests confirmed that there is a significant association between inhibition and responsiveness to painful stimulation (Table 2). Most of these tests used a correlational approach (48 tests), of which again one-third showed that a reduced ability to in-

hibit is significantly correlated with a higher responsiveness to experimental pain (e.g., a higher pain intensity rating, a lower pain threshold, or a lower pain tolerance). The effect size for this correlation, however, was only small (Figure 2). Three out of six studies showed that pain responsiveness was significantly reduced when performing an inhibition task (executive functioning → pain). None of the studies (3 out of 3) found evidence for a significant reduction in inhibition performance when simultaneously receiving painful stimulation (pain → executive functioning). For the interference design, no effect sizes could be computed given the lack of reported data in the respective studies.

Updating – Experimental-Pain Studies

Several tests were frequently used to measure updating, including the N-back task, Digit Span backward, and the OSPAN task (see Table 4). In total, 17.5% of all 57 tests confirmed that there is a significant association between updating and responsiveness to experimental pain (Table 2). Most of these tests used a correlational approach. However, only 4.4% of these correlational tests showed that higher responsiveness to painful stimulation is significantly correlated with reduced updating performance (2 out of 46 tests). The effect size for this correlation was negligible (Figure 2). In contrast, all interference studies conducted to investigate whether pain responsiveness changes when simultaneously performing an updating task (executive functioning → pain), showed that pain responsiveness is significantly reduced in this situation (3 out of 3 tests). Similarly, 4 out of 8 interference studies demonstrated that updating performance is significantly reduced when simultaneously receiving painful stimulation (pain → executive functioning). Again, effect sizes for the interference designs could not be computed.

Shifting – Experimental-Pain Studies

Shifting was assessed using a variety of different tasks (e.g., Trail Making Task B, attentional switching task, Plus-minus) (see Table 4). In total, 4 of the 16 tests confirmed that there is a significant association between shifting and responsiveness to painful stimulation (Table 2). Only 15.4% of the tests using a correlational approach showed that higher responsiveness to experimental pain is significantly correlated with reduced shifting performance (2 out of 13 tests). The effect size was also negligible (Figure 2). Two out of three tests showed that painful stimulation significantly reduces shifting performance in an interference design (pain → executive functioning). No study investigated whether performing a shifting task reduces responsiveness to painful stimulation (executive functioning → pain). Effect sizes for the interference designs could not be computed.

Pain inhibition – experimental-pain studies

In the context of this review, one type of pain responsiveness might be especially interesting, namely, the ability to inhibit pain. The ability to inhibit pain may be closely linked to a general ability to inhibit cognitive and behavioral responses (as assessed with neuropsychological tests). The ability to inhibit pain is most often measured using the conditioned pain modulation (CPM) paradigm, which refers to the process whereby one painful stimulus inhibits the perception of a second painful stimulus. Our results show that this endogenous pain inhibition seems to be especially associated with cognitive inhibitory functioning. In total, 45% of all tests performed showed that poor pain inhibition is significantly correlated with poor cognitive inhibition (5 out of 11 tests), with an average correlation coefficient of 0.36 (a small effect size). In comparison, the correlation between pain inhibition and updating performance was less strong, only 10% of the tests performed showed significant associations. The correlation between shifting performance and pain inhibition has not been investigated.

Summary – Experimental-Pain Studies

The findings of studies using experimental pain stimulation partly confirm the findings of chronic-pain studies. The results of studies using an interference design indicate that there is moderate evidence that painful stimulation reduces executive functioning performance, and that responsiveness to experimental pain is reduced when performing an executive task. The results of studies using a correlational approach show that responsiveness to experimental pain can be negatively correlated with executive functioning performance, although evidence for this is very weak. Inhibition shows the strongest association with pain compared to updating and shifting, especially when looking at one specific type of pain responsiveness, namely, the ability to inhibit pain.

Discussion

Executive Functioning and Chronic Pain

With regard to the chronic-pain studies, this review reveals ample evidence for a reduction in executive functioning in chronic pain, despite the heterogeneous patient groups investigated and despite the various tests used to assess executive functioning. On average, one-third of all group comparisons performed showed that executive functioning is significantly reduced in chronic-pain patients, with medium-to-large effect sizes. No study reported an increase in executive functions in chronic-pain patients

compared to pain-free individuals, which corroborates the notion that the demonstrated decline in executive functioning is not simply a false-positive finding. Our findings are in line with previous reviews (Berryman et al., 2013; Berryman et al., 2014; Moriarty et al., 2011), which also found small to moderate impairments in inhibition, updating and shifting ability in chronic-pain patients (Berryman et al., 2013; Berryman et al., 2014).

In contrast to previous reviews/meta-analyses, we not only looked for differences between chronic-pain patients and pain-free controls, we also included studies investigating whether executive functioning performance is correlated with the severity of chronic pain. We found that executive functioning was negatively correlated with self-reported pain intensity across several studies, with stronger pain being associated with worse executive functioning. However, the evidence for this negative correlation is much weaker (average correlation coefficients were negligible) than the evidence for the reduction in executive functions in patients compared to controls. Nevertheless, almost all studies that found evidence for a significant correlation between pain intensity and executive functioning report a negative correlation. Only two studies (2.8% of all tests) report a positive correlation, with one of these studies having been conducted on patients suffering from dementia-related cognitive impairment (Scherder et al., 2008). Given that the ability to validly report pain declines across the course of dementia (Achterberg & Lautenbacher, 2017), the positive correlation between executive functioning and reported pain intensity could be because of the more severely impaired patients not being able to give a self-report of pain.

Taken together, the findings of chronic-pain studies suggest that patients often have impairments in executive functions (moderate effect size), but that these impairments do not increase linearly when pain intensity increases.

Possible Mechanisms Mediating Executive Functioning Impairment in Chronic-Pain Patients

One hypothesis that may explain the executive functioning problems occurring in chronic-pain patients is the theory of limited cognitive resources (Eccleston & Crombez, 1999), which states that the processing of pain demands attention, similar to that demanded to perform an executive task. Because of the attention demanded by pain, there are thus less attentional resources available to perform executive functions (Eccleston, 1995).

Another possibility, but not one excluding the theory of limited resources, is that chronic pain affects executive

functioning via functional and anatomical changes in the brain caused by the chronic pain condition itself (Moriarty et al., 2011). Chronic pain has been found to be associated with several structural changes in the brain, when gray matter declines in the anterior cingulate cortex, the insular cortex, the orbitofrontal cortex, and the dorsolateral prefrontal cortex (Rodriguez-Raecke et al., 2013). Two chronic-pain studies included in this review demonstrated that these structural brain changes correlate with executive functioning performance. Gray matter volumes in the medial frontal cortex and the left middle frontal gyrus were positively correlated with updating performance in fibromyalgia patients (Luerding et al., 2008). Similarly, cortical thickness of the right dorsolateral prefrontal cortex was positively correlated with inhibition performance in patients with complex regional pain syndrome (Lee et al., 2015).

The above-mentioned theories act on the strong assumption that pain is the causal factor leading to a decline in executive functioning, either by limiting the cognitive resources and/or by causing structural changes in the brain. These are, however, only assumptions, given that cross-sectional chronic-pain studies do not allow investigation of the causal direction between executive functions and pain. However, by manipulating pain using experimental pain stimuli, we may be able to better determine the direction of the association between executive functions and pain. The findings of these experimental-pain studies are discussed in the next section.

Executive Functions and Experimental Pain: What Disrupts What?

Interference Design

In an experimental setting, it is possible to investigate the effect of simultaneously receiving painful stimulation while performing an executive functioning task. This condition is then compared with a control condition, in which participants only perform an executive functioning task and/or only receive painful stimulation. The results of the interference design studies included in this review suggest that pain does indeed interfere with executive functioning and vice versa. By letting the participants perform an executive task twice, once while receiving painful stimulation and once without receiving painful stimulation, roughly 40% of the studies demonstrated that painful stimulation reduces executive functioning performance (especially for the domains “updating” and “shifting”). This proves the causal direction of pain leading to a decline in executive functioning, which is assumed by the studies on chronic pain. At the same time, the findings of the interference design studies also show that performing

an executive task can reduce pain responsiveness, though this is not exclusively the case for executive tasks. Distraction generally reduces pain, so that other cognitive tasks besides executive function tasks can also reduce pain responsiveness (Dowman, 2004; Frankenstein et al., 2001). Interestingly, pain-related brain activation also declines significantly when participants simultaneously perform an executive functioning task while receiving painful stimulation (Bantick et al., 2012; Coen et al., 2008; Seminowicz et al., 2004; Seminowicz & Davis, 2007; Valet et al., 2004). Thus, in clinical practice, chronic patients should be encouraged to engage in cognitively stimulating and entertaining tasks or activities, since these have the capacity to distract from the pain.

Correlational Design

In recent years, the association between executive functioning and pain has been suggested to be even more complex, because it has been suggested that declining executive functioning might be associated with a higher sensitivity to pain and a worse ability to cope with pain – and therefore be a risk factor for higher vulnerability to developing chronic pain. Evidence that reduced executive functioning might be a risk factor for a higher pain sensitivity came from a recent longitudinal study investigating whether executive functioning performance before the start of a surgery can predict the extent to which people suffer from pain after surgery (Attal et al., 2014). The study showed that poorer executive functioning performance predicts pain intensity up to a year after the surgery. Evidence supporting this assumption of a link between pain sensitivity and executive functioning stems from correlational analyses, usually conducted in pain-free individuals. This review shows that executive functioning can correlate negatively with responsiveness to experimental pain. However, the association is only weak, given very small effect sizes and the low number of studies that found a significant correlation (20%). Nevertheless, all significant findings were in the same direction of a negative correlation. Interestingly, the association becomes much stronger in those studies that use a specific type of pain response, namely, the pain inhibitory response (conditioned pain modulation) and correlate it with cognitive inhibition (e.g., Stroop task). Here, 45% of the correlations performed show that poor pain inhibition is correlated with poor cognitive inhibition. Thus, it might not be the pain responsiveness that is linked to executive functioning, but rather certain aspects of the pain response system (e.g., the ability to inhibit pain).

Together, the different study designs used by experimental-pain studies suggest that not only does pain disrupt executive functioning, there might also be a shared underlying mechanism (see below), with poorer execu-

tive functioning being a risk factor for higher vulnerability to pain.

The Frontal Cortex as Underlying Mechanism

One candidate for the idea of a shared underlying mechanism might be the frontal cortex. As discussed above, chronic-pain patients can show structural brain changes in the frontal cortex which correlate with executive functioning performance (Lee et al., 2015; Luerding et al., 2008). The role of the frontal cortex in pain is supported by findings of animal studies showing that pain can lead to changes in neuronal morphology (Metz et al., 2009) and a decrease in neuronal activation (Ji et al., 2010) in the frontal cortex. Of course, the frontal cortex is a broad area that can be divided into multiple subregions. Regarding the link between executive functions and pain, two regions might be of particular interest: (1) the *orbitofrontal cortex* and (2) the *dorsolateral prefrontal cortex*.

The orbitofrontal cortex is suggested as playing a substantial role in the ability to inhibit pain. This notion is based on observations of increased activation of the orbitofrontal cortex during different pain inhibition tasks (Bantick et al., 2012; Moont et al., 2011; Valet et al., 2004). Besides being involved in pain inhibition, the orbitofrontal cortex is also involved in executive functioning, especially in inhibitory functioning (Collette et al., 2005). Thus, our finding of a significant positive correlation between cognitive inhibition and pain inhibition could be moderated by the orbitofrontal cortex.

The dorsolateral prefrontal cortex is involved in the ability to cope with pain (Gracely et al., 2004; Seminowicz & Davis, 2006; Seminowicz et al., 2013). Pain-coping skills are important because maladaptive coping can increase pain intensity and can be a risk factor for the development of chronic pain (Sullivan et al., 2001). Beyond being involved in pain coping, the dorsolateral prefrontal cortex is also involved in various domains of executive functioning (Jurado & Rosselli, 2007). Thus, dorsolateral prefrontal functioning can affect both the ability to cope with pain as well as executive performances.

In summary, poor functionality of the frontal cortex can result in poor executive performances as well as in high responsiveness to pain, possibly because of (1) limited pain inhibition as a consequence of reduced orbitofrontal functioning and/or (2) limited pain-coping skills as a consequence of reduced dorsolateral prefrontal functioning. A clinical implication of this assumption is that chronic-pain patients might benefit from strengthening frontal capacities, for example, by executive functioning training, to strengthen the system's ability to better in-

hibit pain as well as better cope with pain. It should be tested in future research whether this would make individuals less vulnerable to pain.

The Role of Depression

Given that depressive symptoms are prevalent in chronic-pain patients and have been shown to be associated with executive functioning deficits (Rock et al., 2014), it possible that the link between pain and executive functioning might also be moderated by depressive symptoms. Being aware that depression is associated both with pain as well as with deficits in executive functioning, most chronic-pain studies included in this review (approximately 65%) did assess the level of depressive symptoms. Upon testing whether depressive symptoms might explain the relation between chronic pain and executive functioning, three studies found confirming evidence (Gijzen et al., 2011; Jongma et al., 2011; van der Leeuw et al., 2016). However, even more studies failed to show that depressive symptoms can explain the executive functioning deficits in chronic-pain patients (Abeare et al., 2010; Akdoğan et al., 2013; Armstrong et al., 1997; Dick et al., 2002; Glass et al., 2011; Grace et al., 1999; Grisart & Plaghki, 1999; Hall et al., 2011; Ickmans et al., 2015; Karp et al., 2006; Legaretta et al., 2016; Luerding et al., 2008; Miró et al., 2011; Murata et al., 2017; Park et al., 2001; Weiner et al., 2006). Therefore, depressive symptoms seem to play only a minor role in the association between chronic pain and executive functioning.

Limitations

An important limitation of this systematic review is the heterogeneous patient group investigated. We decided to include many different pain conditions, in order to give a comprehensive overview of the findings on the relationship between executive functioning and pain. When compiling the outcomes, we did not differentiate between different types of pain, although different types of pain can be expected to have a different impact on executive functions. However, the limited number of studies and the diversity of executive functioning tests being used did not allow for a more differentiated approach. Nevertheless, a distinction between different pain types seems reasonable. An interesting example for the need for differentiation between different types of pain is the concept of *cogniphobia*: Patients with frequent (posttraumatic) headaches and with mild traumatic brain injury have been found to avoid cognitive tasks because of fear of developing or increasing pain (Silverberg et al., 2017; Suhr & Spickard, 2012). Thus,

in a testing situation it should be taken into account that *cogniphobia* might exist in certain types of pain, which can decrease cognitive performance.

Another limitation is that many studies failed to report in detail the analgesic medication use in the chronic-pain patient group, which was revealed by the risk of bias assessment. This would have been important because opioid use can have an effect on cognition, including executive functions (Baldacchino et al., 2014).

Conclusion

In conclusion, this review shows that there is moderate to strong evidence that executive functions are decreased in chronic-pain patients, and that these executive dysfunctions do not linearly increase with the pain intensity. The findings of experimental-pain studies suggest that there might be a bidirectional relation between pain and executive functioning: Pain not only disrupts executive functioning, but poorer executive functioning may be a (small) risk factor for higher vulnerability to pain. Changes in the frontal cortex of the brain, especially in orbitofrontal and dorsolateral regions, might moderate this association.

Electronic supplementary material

The electronic supplementary material (ESM) is available with the online version of the article at <https://doi.org/10.1024/1016-264X/a000264>

ESM 1. Table S1. Risk of bias assessment chronic pain studies

ESM 2. Table S2. Risks of bias assessment experimental pain studies

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