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Systematic Review

An Overview of Offset Analgesia and the Comparison with Conditioned Pain Modulation: A Systematic Literature Review

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Background: Offset analgesia (OA) is an increasingly described phenomenon to measure endogenous pain inhibition, in which a greater decrease in pain intensity is experienced than would be predicted by the decrease in painful stimulation. The temporal filtering in this OA phenomenon differs from the spatial filtering in the commonly described conditioned pain modulation (CPM). Yet, the knowledge on the efficacy of OA in chronic pain patients is scarce, compared to CPM efficacy.

Objective: This systematic review has been conducted to provide an overview of the current knowledge regarding OA, and to compare it to CPM.

Study Design: A systematic review of research studies that investigated the application or mechanisms of OA.

Setting: The present study took place at Ghent University and the University of Antwerp.

Methods: This systematic review follows the PRISMA guidelines. The electronic databases Pubmed and Web of Science were searched in January 2015. Full text clinical reports addressing OA were included. The checklists for randomized controlled trials, case-control studies, and cohort-studies provided by the Dutch Institute for Healthcare Improvement and the Dutch Cochrane Centre were used to assess methodological quality. The articles received a level of evidence A1, A2, B, C, or D, based on study design and risk of bias. These levels were used to determine the strength of conclusion (level 1 to 4).

Results: Seventeen articles met the inclusion criteria. Sixteen studies used quantitative sensory testing to provoke OA; however, differences in protocols are present. OA can function as a non-opioid mediated assessment tool for endogenous pain inhibition, and activates brain regions such as periaqueductal gray (PAG), dorsolateral prefontral cortex, insula, medulla, pons and cerebellum, indicating strong brain derived pain modulation. The primary somatosensory cortex is, conversely, less activated during OA. OA is decreased in neuropathic patients. Nonetheless, evidence for the influence of individual factors on OA is limited. OA and CPM seem to rely on different mechanisms.

Limitations: Search strategy was taken wide, wherefore a large variety of research perspectives were included.

Conclusions: This systematic review displays OA as a temporal filtering mechanisms that is more brain-derived compared to the spatial assessment method CPM. There is strong evidence for reduced OA in neuropathic patients, however, evidence regarding OA in (sub)acute and central sensitization patients, and the influence of personal factors on OA is currently scarce and needs further investigation.

Key words: Endogenous pain inhibition, pain modulation, OA, temporal filtering, CPM, spatial filtering, pain pathways

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Chronic pain is a widely described phenomenon. Prevalence figures reveal that approximately 19% of the European adult population is a target of chronic pain (1). In various chronic pain states, central pain modulatory pathways are affected. More specifically, dysfunctions of descending modulatory pathways are likely to lie at the basis of many chronic pain syndromes. Syndromes with already proven dysfunctional acting descending modulatory pathways include fibromyalgia (2-4), chronic fatigue syndrome (5,6), irritable bowel syndrome (7), complex regional pain syndrome (8), temporomandibular disorder (7), and whiplash associated disorders (9).

Conditioned pain modulation (CPM) is commonly used as an assessment tool for measuring endogenous pain inhibition in current pain research (5,10,11). Reduced CPM-effects in central sensitization patients are extensively reported in the literature (5,9,12). CPM is a type of spatial filtering, measuring in particular diffuse noxious inhibitory controls (DNIC). In this paradigm, a painful stimulus applied to a distant area of the body (= conditioning stimulus), inhibits the pain response of another noxious stimulus (= test stimulus) (13-15).

Another increasingly described method for measuring endogenous pain modulation is offset analgesia (OA). OA is the larger decrease in perceived pain intensity than would be predicted by the small decrease in noxious stimulation. This small decrease in noxious stimulation is set with the same device, at the same place of the body. Therefore, dissimilar from the spatial filtering in CPM, OA is probably operating as a temporal filtering mechanism (16). OA can be defined as a greater decrease in pain intensity when going from a noxious painful stimulus (T2) to an unpleasant stimulus (T3) than can be expected from the increase of pain intensity when transitioning from an unpleasant stimulus (T1) to a noxious painful stimulus (T2) (definition of OA, first described by Grill and Coghill (17)). This OA paradigm is presented in Fig. 1a. The large change in pain intensity during OA is different from the adaptation and/or habituation that could occur during prolonged and/or repeated noxious stimulation (18,19). Accordingly, OA magnitude is measured by the largest VAS score at T2 – the lowest VAS score at T3, compared to the decrease in VAS rate during the control trial, presented in Fig. 1b. Although this definition is rather delineated, the exact mechanisms in OA are still unknown.

OA and CPM are 2 paradigms, activating endogenous pain inhibition, that are often used as assessment tools in pain research. Although they seem to rely on a different rationale, the exact relation or difference between CPM and OA remains unclear. Especially, since different OA protocols are used and the knowledge on the efficacy of OA in chronic pain patients is scarce, compared to CPM efficacy. This systematic review has been conducted to provide an overview of the current

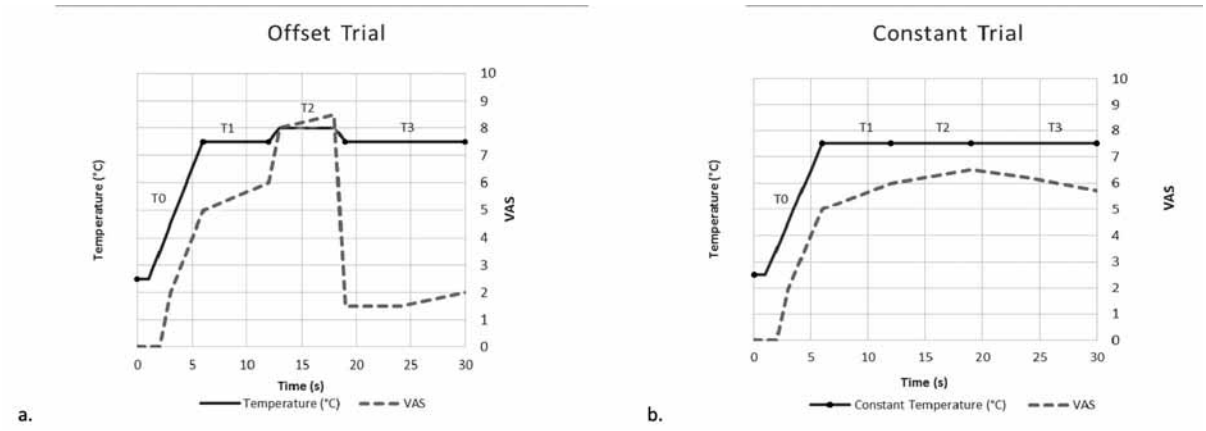

Fig. 1. Time period:
T0: baseline temperature; temperature starts at baseline and increases to test temperature
T1: unpleasant test temperature
T2: painful stimulation
T3: unpleasant test temperature
VAS: Visual Analogue Scale

knowledge regarding OA, and to compare it to CPM. Unravelling such paradigms may steer further insight into the exact mechanisms behind (the failing of) endogenous pain inhibition.

Methods

This systematic review is reported following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines (20).

Research Question

In order to conduct this systematic review, the Patient-Intervention-Comparison-Outcome-approach (PICO) was used. The following PICO-questions were formulated: (1) Which methods (O), in healthy participants, patients, or animals (P), could be used to measure OA (I), as paradigm for the assessment of endogenous pain inhibition? (2) Which mechanisms (O) are triggered by OA (I) in healthy participants, patients, or animals (P)? (3) Are there personal factors (P) influencing the endogenous pain inhibition (O) measured by OA (I)? (4) Can OA (I) be used to measure inefficient endogenous pain inhibition (O) in patients (P)? (5) Is OA (I) related to the same mechanisms (O) as CPM (C) to establish endogenous pain inhibition in healthy participants, patients, or animals (P)?

Search Strategy

The databases PubMed and Web of Science were searched in January 2015 using a combination of search terms. Key words and mesh terms were listed for each part of the PICO and are represented in Table 1. Search terms for I were placed between quotation marks, besides, I without quotation marks was combined with the search terms formulated for C or O using the Boolean operator 'AND.' Various synonyms of the search terms for C and O were entered using the Boolean operator 'OR.' Hand searching was performed by reading the reference lists of the included articles based on full text.

Eligibility Criteria and Study Selection

Search results of the PubMed and Web of Science databases were screened on title and abstract according to the inclusion and exclusion criteria presented in Table 2. All inclusion criteria had to be fulfilled. The full text of the remaining articles was retrieved if title and abstract were considered potentially eligible. Each full text article was evaluated once again for eligibility based on the inclusion criteria. Literature was screened independently by 2 researchers (EV and EB), both master of science in rehabilitation sciences and physiotherapy, and trained in conducting systematic reviews by the last author (MM), who obtained a PhD and published several systematic reviews in the domain of central sensitization.

Study Quality and Levels of Evidence in Individual Studies

The risk of bias, and additionally the quality of the used OA paradigm, were assessed for each included study.

Two researchers (EV and EB) independently examined the quality of the study designs using the checklists of risk of bias developed by EBRO-platform, provided by the Dutch Institute for Healthcare Improvement (CBO) and the Dutch Cochrane Centre (http://dcc.cochrane.

Table 1. Key words.

Population	Intervention	Comparison	Outcome
Healthy	Offset analgesia	Conditioned pain modulation	Endogenous pain
Patients	Psychophysical testing paradigms	CPM	Inhibition
Animals	Endogenous analgesia	Pain-inhibits-pain	Pain (Mesh)
		Diffuse noxious inhibitory control	Pain evaluation
		DNIC	Pain threshold (Mesh)
		Counter-irritation	Pain management (Mesh)
		Counter stimulation	Pain measurement (Mesh)
		Heterotopic Noxious Conditioning Stimulation	Analgesia (Mesh)
		HNCS	

Table 2. *Inclusion and exclusion criteria.*

Selection criteria	Inclusion criteria	Exclusion criteria
Population	Humans, animals, healthy subjects and patients	
Intervention	Topic: Application of Offset Analgesia or mechanisms of Offset Analgesia	Topic not examining application of Offset Analgesia or mechanisms of Offset Analgesia
Outcome	Endogenous pain inhibition	Topic not examining endogenous pain inhibition
Design	Clinical reports	Non-clinical reports such as letters to the editor, editorial, reviews
Article type	Full text reports	Abstracts, posters
Language	English, French, Dutch	Other

Table 3. *Scoring on the RCT checklist.*

	Martucci, Yelle et al, 2012	Martucci, Eisenach et al, 2012	Niesters, Dahan et al, 2011	Niesters, Hoitsma et al, 2011	Niesters and Proto et al, 2014
	CROSS OVER DESIGN = RCT checklist				
1. Allocation randomized?	1	1	1	1	1
2. Blinded randomization?	NSI	NSI	NSI	NSI	1
3. Patients blinded for treatment?	1	1	1	1	1
4. Blinded treatment officer?	0	0	0	0	1
5. Blinded effect assessor?	NSI	NSI	NSI	NSI	1
6. Comparable groups?	1	1	1	0	1
7. Loss to follow up	1	1	1	1	1
8. Intention to treat analysis	1	1	1	1	1
9. Comparable treatment?	1	0	1	0	1
Total score	6/9	5/9	6/9	4/9	9/9
Level of Evidence	B	B	B	B	A2

Answer possibilities: Yes = 1 point; No = 0 points; No sufficient information (NSI) in article to answer (no info) = 0 points; NA = Not applicable = item is not included in total score

org/). Depending on the study design, the checklist for randomized controlled trials (RCTs), case-control, or cohort studies was used. Each checklist assessed 6 to 9 criteria or items, which are displayed in Tables 3 – 5.

The fulfillment of each item on the checklists was answered by either a yes (= 1 point), no, or lack of information (= 0 points). The majority of studies did not use a control group, but instead all participants underwent a test protocol and a control protocol. In that case, criteria related to the control group were interpreted as criteria for the control protocol. Studies were awarded 1 point for confounding factors, if at least 2 of following factors were taken into account: gender, age, menstrual cycle, catastrophizing, anticipation (e.g., attention, expectations), genetics, or medication, based on a previous systematic review about the influence of personal factors on CPM (21).

The scores of the 2 researchers were compared, and in case of disagreements, a consensus meeting was held to achieve agreement between the researchers. In case the disagreement could not be resolved, a third decisive opinion was provided by the first author (LH), who is a PhD candidate in pain research and has (co-) authored several published systematic reviews.

The levels of evidence were assigned to the included articles using the EBRO-guidelines of the Dutch Institute for Healthcare Improvement. According to study design and risk of bias, the articles received a level of evidence A1 (= systematic review of at least 2 independent studies), A2 (= randomized, double blinded, comparative,

clinical research with sufficient sample size and good methodological quality), B (= comparative research, missing at least one feature for A2, for example patient-control and cohort studies), C (= non-comparative research) or D (= experts opinion). These levels were used to draw and determine the strength of conclusion which varied between 1 and 4. With level 1 standing for the conclusion of at least one A1, or full consensus of at least 2 independent A2 studies; level 2 indicates one study A2 or full consensus of at least 2 independent studies with level B; level 3 for at least one article of level B or C or when results are conflicting; and level 4 when the conclusion is based on experts' opinion.

Additionally, a checklist for the OA paradigm was made to verify if the protocol was sufficiently described. Six items were set up as criteria to define a good description of the protocol. The fulfillment of each item was answered by either yes or no, corresponding to respectively one or zero points.

Data Items and Collection

Information was extracted from each included full text article and summarized in an evidence table. The following items were collected: population (healthy participants or patients), characteristics population (sample size, gender distribution, age distribution), study objective, test protocol and devices, control protocol, results and conclusion, and *P*-value.

Table 4. *Scoring on the cohort checklist.*

	Suzan et al, 2014
COHORT DESIGN = cohort checklist	
1. Study group well defined?	1
2. Selection bias?	1
3. Sufficient description of exposed factor?	1
4. Well defined outcome measurement?	1
5. Blinded outcome measurement?	NA
6. Follow up?	1
7. Selective loss-to-follow-up	1
8. Confounders?	0
Total score	6/7
Level of evidence	B

Answer possibilities: Yes = 1 point; No = 0 points; No sufficient information (NSI) in article to answer (no info) = 0 points; NA = Not applicable = item is not included in total score

Table 5. *Scoring on the case-control checklist.*

	Derbyshire et al, 2008	Derbyshire et al, 2009	Grill et al, 2002	Hamaguchi et al, 2013	Honigman et al, 2013	Naugle et al, 2013	Yelle et al, 2008	Yelle et al, 2009	Ruscheweyh et al, 2014	Nahman-Averbuch et al, 2014	Naugle and Riley et al, 2014
CASE CONTROL / CROSS SECTIONAL DESIGN = case-control checklist											
1. Sufficient description test group?	0	0	0	1	1	1	1	1	1	1	1
2. Sufficient description control group/protocol a?	1 a	0 a	1 a	1 a	1 a	1	1 a	1 a	1	1 a	NA
3. Selection bias?	NA	NA	NA	NA	NA	0	NA	NA	1	NA	1
4. Sufficient description of OA protocol?	1	1	1	1	1	1	1	1	1	1	1
5. Blinded measurement of exposed factor?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
6. Confounders?	0	0	0	1	1	0	0	0	1	1	1
Total score	2/4	1/4	2/4	4/4	4/4	3/5	3/4	3/4	5/5	4/4	4/4
Level of Evidence	B	B	B	B	B	B	B	B	B	B	C

Answer possibilities: Yes = 1 point; No = 0 points; No sufficient information (NSI) in article to answer (no info) = 0 points; NA = Not applicable = item is not included in total score

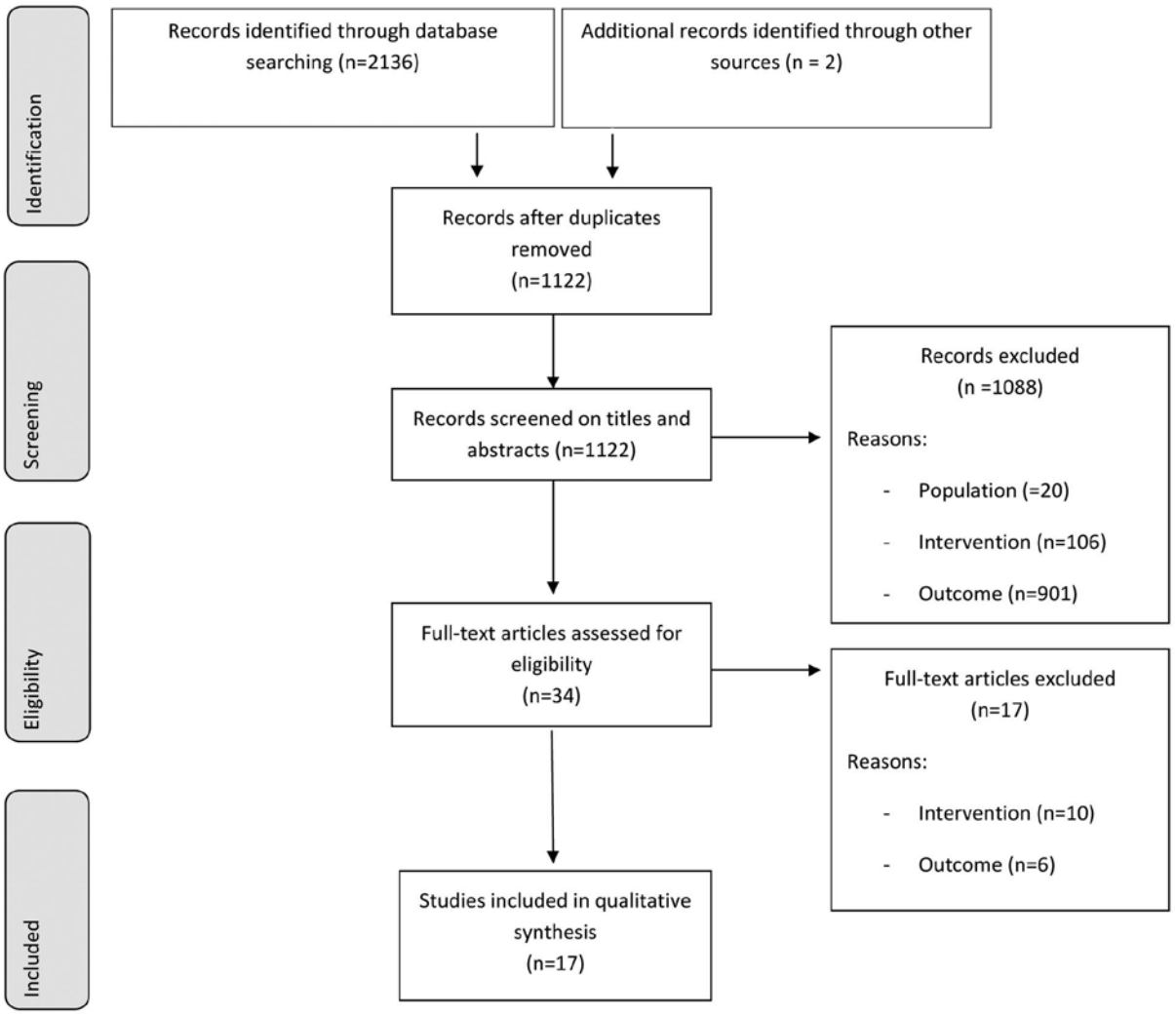

Fig. 2. *Flow chart study selection process.*

Results

Study Selection

The selection process is drafted in Fig. 2. Seventeen articles were included, including 5 RCTs (22-26), 10 case-control studies (16,17,27-34), one cross-sectional study (35), and one prospective cohort study (36).

Study Quality and Levels of Evidence within Studies

Tables 3, 4, and 5 show the results for the risk of bias. A consensus meeting was necessary as for 24% of the scored items the 2 researchers did not agree. After negotiation with the third researcher, full agreement was achieved.

Four out of 5 RCTs failed to blind the therapists, as they had to observe the occurrence of side effects (e.g., nausea, vomiting, drowsiness) (22-25). For blinding the effect assessor, all studies, except one (26) lost points given the fact that analyzation of the results was not blinded. Only the study of Niesters et al (26) was able to blind the effect assessor by blinding the research team until OA responses had been analyzed.

Additionally, 5 out of 12 studies (11 case-control

and one cross-sectional) (29,30,33-35) took at least 2 factors into consideration, all other studies lost points for this item as well.

One RCT received a level A2 (26), 4 RCTs were downgraded to level B due to lack of blinding (22-25). Ten case-control studies (16,17,27-34) and one cohort study (36) obtained a level B. One cross-sectional study (35) was not being comparative and therefore received a level C.

As 2 articles (25,28) scored below 50% on the methodological quality checklist, prudence is warranted when drawing conclusions from these articles.

Table 6 shows the results for the quality of the OA paradigms. All articles defined the OA paradigm well, resulting in scores between 5 and 6 out of 6.

Study Characteristics

Collected data from all studies are shown in Table 7. Fourteen studies investigated OA in healthy participants, with sample sizes ranging from 10 (16,24) to 110 volunteers (25). Four studies explored OA efficiency in patients (25,26,33,36), with sample sizes ranging between 20 (25) and 30 participants (33,36). None of the included studies examined OA in animals. Sixteen out of 17 protocols used a thermal stimulus to evoke OA, only Hamaguchi et al (29) induced OA with a pressure stimulus. Only one study (27) examined which individualized temperature provokes the largest OA-effect and another study (31) examined the influence of assessment site on OA-effect. Ten studies (16,17,22,23,27,28,30,32-34) included a constant pain trial (Fig. 1b) besides the OA trial.

In 9 studies (22,23,26-28,30,34-36) an extra trial besides the offset and constant trial was used. Five studies (22,23,27,28,30) conducted a baseline trial to determine whether pain ratings would differ between 1°C decrease in the OA trial and decreasing to baseline temperature. CPM was additionally assessed in 6 studies (24,26,30,34-36). Two studies (16,17) investigated the time-course of OA.

Twelve studies tried to find out which mechanisms are underlying OA. Naugle et al (31) explored whether

Table 6. *Scoring OA paradigm.*

Study	Derbyshire et al, 2008	Derbyshire et al, 2009	Grill et al, 2001	Hamaguchi et al, 2013	Honigman et al, 2013	Martucci, Yelle et al, 2012	Martuci, Tong et al, 2012	Naugle et al, 2013	Niesters, Dahan et al, 2011	Niesters, Hoitsma et al, 2011	Yelle et al, 2008	Yelle et al, 2009	Nachman-Averbuch et al, 2014	Naugle and Riley et al, 2014	Niesters and Proto et al, 2014
1: test protocol clearly described to be reproducible?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
2: used device and stimulus form clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3: stimulated area clearly described?	1	1	1	1	1	1	0	1	1	0	1	0	1	1	1
4: duration of administering stimulus clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5: outcome measurement and clinimetrics clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
6: eventual results and analysis clearly described?	1	1	1	1	1	1	1	1	NSI	1	1	1	1	1	1
Total score	6/6	6/6	6/6	6/6	6/6	6/6	5/6	6/6	5/6	5/6	6/6	5/6	6/6	6/6	6/6

Answer possibilities: Yes = 1 point; No = 0 points; No sufficient information (NSI) in article to answer (no info) = 0 points; NA = Not applicable = item is not included in total score.

Table 7. *Evidence table.*

Study	Population	Study objective	Test protocol	Control protocol OA	Results	*P*-value/ Z-score
Derbyshire and Osborn, 2008	- 16 healthy subjects - 3 m /13 f - 19-31 yrs (mean age 22 yrs)	OA vs attenuation	Procedure: - 3x OA trial: B(5s) → ITT(5s) → + 1°C (5s) → -1°C (5s) - 3x constant trial: B (5s) → ITT (15s) - 3x baseline trial: B (5s) → ITT (5s) → + 1°C (5s) B (5s) - Demonstration - Thermal stimuli; volar surface of both forearms - B: 35°C - (ITT) B +1°C → 5/20, 10/20, 15/20 GPS (=stop) (5X) → mean = final 3X → 2min rest + repeat other forearm - procedure on 3 separate days repeated Devices: - 27mm diameter peltier thermode - Gracely intensity scale (GPS)	OA 5/20 GPS OA 10/20 GPS OA 15/20 GPS	- interaction of OA with attenuation - within session adaptation exaggerated OA effect, but OA >> effect of within-session adaptation for high pain trials	$P < 0.05$
Derbyshire and Osborn, 2009	- 12 right handed subjects - all f - mean age 23yrs	Objectifying via fMRI descending inhibitory control induced by OA	Procedure: - OA trial: B (6s) → low (41°C)/high (45°C) (6s) → + 1°C (6s) → -1°C (6s) - constant trial: B (6s) → low (41°C)/ high (45°C) (18s) - baseline trial: 35°C (6s) → low (41°C)/ high (45°C) (6s) → + 1°C (6s) → B (12s) - Demonstration - Thermal stimuli; volar surface of both forearms - B: 35°C Devices: - fMRI - 27 mm diameter peltier - Online sliding scale	OA low 41°C OA high 45°C	- PAG; RVM → during OA - thalamus; MCC; pACC; inf. Parietal cortex; S1; S2; Prefrontal cortex → during constant trial	Z-score -3.2 $P < 0.05$ $P < 0.05$
Grill and Coghill, 2002	- 12 healthy subjects - 7 m/5 f - 22-31 yrs	To analyze if active OA exists	Procedure: - OA trial: B →T1 (47,48 or 49°C; 5s); T2 (1,2 or 3° increase; 5s) and T3 (47,48 or 49°C;20s) - constant trial: (35, 47, 48, and 49°C; 35s) - baseline trial: T1 (47, 48, and 49°C;5s) ; T2 (1,2 or 3° increase; 5s) T3; 35°C;20s) - Thermal stimuli; ventral surface of dominant forearm - B: 35°C Devices: - 16x16 mm peltier device - mechanical VAS	- is ≠ pain intensity by 1/2/ 3°C decrease =/≠ to step down to innocuous temperature →baseline procedure: = T1 and T2 T3 = B	- OA effect by 1/2/3°C decrease - no effect T2 size step - + 1°C: eVAS 271% greater than -1°C – OA reversed by 15s continued noxious stimulus	$P < 0.0227$ $P = 0.2024$
Hamaguchi et al, 2013	- 45 healthy subjects - 33 m/12 f - 20-26yrs - right handed	Brain activation during colonic distention by initial mild stimulation vs mild stimulation preceded by intense stimulation	Procedure: - OA trial: sham stimulation (0mmHg) → 40mmHg (80s), 10min. in between - 6 ≠ stimuli patterns - cleanse colons, fasting, testing at 08,15u next day Devices: - Colonoscope inserted + splinting device - PET scan - Ordinate scale	/	Increased brain activity during OA: - PAG - left insula - cerebellum	 Z = 4.68 Z = 4.39 Z= 3.63

Table 7. (cont.) *Evidence table.*

Study	Population	Study objective	Test protocol	Control protocol OA	Results	*P*-value/ Z-score
Honigman et al, 2013	- 29 healthy subjects - 15 m/14 f - 20-40yrs (mean age ± SD: 27,6 ±3,4 yrs)	Examine inter-relation OA and CPM and effect of gender	Procedure: - OA trial: B → 49°C (5s) → +1°C (5s) → -1 °C (20s) - constant trial: 49°C (30s) - CPM trial: tonic noxious heat stimulus 49°C (30s) OA trial: 49 °C (5 s) → 50 °C (5s) → 49°C (20s) Conditioning stimulation: non dominant hand in water bath up to the wrist (60s) - baseline trial: B→ 49°C (5s) → +1°C (5s) → B (20s) - Thermal stimuli; volar surface of the forearm of dominant hand - Training session: 6 short (4s) heat stimuli 45-50°C → tonic heat stimulus 46°C (30s) → non-dominant hand into hot water bath 46°C (15s) - B: 35°C Devices: - 16x16 mm Peltier - Numerical pain scale (NPS)	/	- CPM additional effect on OA in m - OA additional effect on CPM in m	*P* = 0.003 *P* = 0.07
Martucci and Yelle et al, 2012	- 23 healthy subjects - 9 m/ 14 f - 26.3 ± 0.7 yrs - 16 white, 2 black, 2 Asian, and 3 Hispanic subjects.	To investigate if OA is disrupted by experimentally induced peripheral sensitization	Procedure: - OA trial: B →49°C (4-7s) → +1°C (4-6s) → -1°C (30s) - constant trial: 49°C (40s) - baseline trial: 49°C (6-8s) → +1°C (5-9s) → B (30s) - min 2ds in between - assessing areas of mechanical allodynia after removal of the cream and after rekindling stimulus → primary region: 30x30 mm² forearm = preheated area; secondary region: area surrounding primary region with positive response to Von Frey stimuli - training session procedure: 32 heat stimuli 35-49°C (5s) → individual sensitivities (main 49°C) → 45°C (5 min) = marked preheated region → capsaicin cream + transparent dressing → after 30 min remove cream → 10 min rest → 40°C (5 min) to primary region - B: 35°C Devices: - areas of mechanical allodynia: Von Frey filament (2.0 g) - training session: 30 x 30 mm² probe - OA paradigm: 16x 16 mm² Peltier device - eVAS	- training = test but: placebo cream and 40°C preheating stimulus - OA paradigm: = test procedure	- OA independent of peripheral sensitization - OA independent of heat-only sensitization	*P* = 0.0860 *P* = 0.5640
Martucci and Eisenach et al, 2012	- 19 healthy subjects - 11 m/8 f - 25 ± 5.9 yrs - 2 black, 17 white - 8 control subjects from original group (5 m/ 3f); 27 ± 7.9 yrs	OA magnitude after naloxone, exogenous opioids and opioid-induced hypersensitivity	Procedure: - OA trial: B → 49°C (5s) → +1°C (5s) → -1°C (20s) - constant trial: 49 °C (30s) - baseline trial: 49°C (5s) → +1°C (5s) → B (20s) - B: 35°C - Training session: familiarizing using VAS → 35°C (5s) → 45°C (5s) → 49°C (5s) - Thermal stimulus; lower left leg Test alterations in VAS fall rates: 4 short-duration stimuli (49 °C, 4-6s) varying fall rates of 0.5 °C/s or 5.0 °C 4) Peripheral IV catheter right arm → naloxone/remifentanil; 1w apart Devices: - 16 x 16 mm² Peltier device - Sliding scale nonelectric VAS	- Thermal testing: = test without infusion → assess effects of repeated heat testing	- OA largely opioid-independent - thermal hyperalgesia potentiates OA	*P* = 0.3211 *P* = 0.0026

Table 7. (cont.) *Evidence table.*

Study	Population	Study objective	Test protocol	Control protocol OA	Results	*P*-value/ Z-score
Naugle et al, 2013	- 25 healthy younger adults 10 m/15 f; 18–27 yrs - 20 healthy older adults; 9 m/ 11 f; 58–77 yrs	To examine if OA magnitude is reduced in older adults. Does OA differ between m and f	Procedure: - OA trial: 32°C → ITT (15s) → + 1°C (forearm)/ 0.5°C (palm) (5s) → ITT (10s) - Video describing experimental procedure - ITT: thenar eminence of the palm and volar forearm: 42°C + 1°C → temperature at which subjects experienced mild to moderate pain (30s heat stimulus) - B: 32°C Devices: - 23 x 23 mm Peltier thermode - eVAS	- Younger adults vs older adults - = test procedure	- peripheral mechanisms initiate OA - peripheral factors may interrupt inhibitory processes regulating OA→ absence OA at the palm - magnitude OA m = f - magnitude OA young > old	 *P* > 0.05 *P* = 0.048
Niesters and Dahan et al, 2011	- 10 healthy subjects - 4 m/6 f	The effect of ketamine on CPM and OA	Procedure: - OA trial: B → ITT (5s) → + 1°C (5s) - 1°C (20s) → B → 3 min rest → repeat 2x - CPM trial: experimental stimulus: B → ITT (heat) (30s) → B 3min rest → repeat 2x Conditioned stimulus: 25s before experimental stimulus → immersion foot and lower leg in cold water - 1h ketamine infusion + 20min wash-out period - Thermal stimuli; volar side of the arm - ITT (heat): 42°C + 1°C → 49°C (10s); 5-10 min rest in between - ITT (cold): 6°C – 18 °C - B: 32 °C Devices: - 3 x 3 cm thermal probe - eVAS	- At least 2 weeks in between - Placebo infusion + 20min wash-out period + OA and CPM (= test)	- ketamine no effect on OA - OA NMDA independent - OA ≠ CPM	*P* > 0.05
Niesters and Hoitsma et al, 2011	- Total: 130 subjects - 110 volunteers, 6-80 yrs - 10 patients with neuropathic pain 2 m/8 f - 10 = healthy controls 2 m/8 f (not from ≈sample)	Explore OA in neuropathic patients Investigate whether age and sex differences exist in OA	Procedure: - OA trial: 32°C → ITT (5s) →+1°C (5) → -1°C (20s) → B → 3min rest → repeat 2x - Each p 3 trials, 2-4wks in between - Randomized 1h placebo/ ketamine/ morphine infusion → 20min wash-out - Thermal stimuli; volar side forearm non-dominant hand - ITT: 42°C + 1°C → lowest temperature eVAS of 50mm; - B: 32°C Devices: - 3 x 3-cm thermal probe - eVAS	- Controls: = but no infusion and ≠ stimuli duration (10s) + 5-10 min rest - OA trial volunteers: 45°C (5s) 46°C (5s) → 45°C (20s).	-No differences between age groups - OA m= f - age-dependent sex-effect in 20+ cohorts - OA decreased in neuropathic p - ketamine/ morphine no effect on OA	*P* = 0.54 *P* = 0.57 *P* = 0.002 *P* < 0.001 *P* 0.51
Yelle et al, 2008	- Test: 12 healthy subjects - - Control: 10 healthy subjects - 23-36 yrs	Explore if OA functions as a temporal filtering mechanism. If OA could inhibit a second noxious heat stimulation (centrally mediated)	Procedure: - OA trial: 49°C (5s) → 50°C (5s) → 49°C (20s) - constant trial: 49°C (30s) - one- temperature paradigm: 4x: 35°C→ 48°C or 50°C (5s) in 5°C/s → 35°C in 0.5/1.0/2.0/3.5 or 5.0 C°/s - Thermal stimuli; volar side forearm non- dominant hand - B: 35°C Devices: - 16-16 mm probe - VAS	= area test - Paired stimulus paradigm 4x: 2 probes 50mm apart → ≠ conditions: 49_49; 3T_3T; 3T_49; 49_3T. 49_35 or 3T_35	- OA = temporal sharpening mechanism → VAS fall rates are faster than predicted by linear relationship - OA has a no summation effect - OA lasts about 15s	*P* < 0.0001 *P* > 0.05

Table 7. (cont.) *Evidence table.*

Study	Population	Study objective	Test protocol	Control protocol OA	Results	*P*-value/ Z-score
Yelle et al, 2009	- 15 healthy subjects - 7 m/8 f - right handed - 21-34 yrs	Examine whether midbrain and brainstem regions are involved in pain modulation evoked by OA	Procedure: 4x 8 stimuli: 35°C-43°C–49°C (5s) → 4 ≠ series: - 2x OA trial: 49°C (6-9s) → +1°C (7-8s) →-1°C (13-17s) - 2x Constant trial: 49°C (30s) - Thermal stimulation; posterior aspect left lower leg - 2h lasting fMRI trial - B: 35°C Devices: - 16 x 16 mm Peltier device - VAS	/	- increased activity during OA: PAG; cerebellum; posterior thalamus; globus pallidus; pons; medulla; insula; DLPFC; MCC; - decreased activity during OA: S1, VMPC	
Nahman-Averbuch et al, 2014	- 13 right-handed subjects - 5 m / 8 f - 25.6 ±2.8 yrs	Is spatial filtering accomplished by similar mechanisms as temporal filtering	Procedure: - 3x OA trial: posterior to lower left leg. 49°C (5s) +1°C (5s) → 49°C (20s) - 3x constant trial: posterior to left lower leg. 49°C (30s) - 3x CPM trial: CS: right foot immersion (10-12°C) (87s) TS: tonic heat to posterior lower left leg (49°C) (30s) - familiarization session; 32 heat stimuli (35-49°C, 5s) on posterior lower leg - B: 35°C Devices: - 16 x 16 mm MRI-compatible thermode probe - cVAS - structural and functional MRI	/	- no difference between OA and CPM magnitude - CPM → reduced activity of thalamus, posterior insula and SII - OA → reduced activity of SI. Increased activity anterior insula, DLPFC, intraparietal sulcus, inferior parietal lobule. - OA vs CPM →CPM reduced activity in brain stem and OA increased activity in brain stem	$P = 0.754$
Naugle and Riley, 2013	- 48 healthy subjects - 24 m / 24 f - 18 – 76 yrs	Determine whether self-reported levels of PA predict pain inhibition assessed by OA and CPM	Procedure: - 3x OA trial: right forearm. 47°C (15s) 48°C (5s) → 47°C (10s) - CPM trial: CS: cold water immersion right foot (10°C – 12°C)(180s) TS: thermal stimulus thenar left palm (response dependent stimulation for 150s) - training session; heat pain threshold and suprathreshold. - TS of heat pain session - B:neutral temperature Devices: - 30 x 30 mm thermode (OA) - 23 mm x 23 mm Peltier thermode (CPM) - eVAS	/	- Self-reported total (14.6%) and vigorous (14.3%) physical activity predict CPM but not OA. - More vigorous and total physical activity exhibit greater CPM	Model P = 0.006 resp. $P = 0.007$ for CPM
Niesters et al, 2014	- 24 patients with diabetic polyneuropathy - Tapentadol group 63 yrs (58 – 67) - Placebo group 64 yrs (57 – 66)	Relies the analgesic efficacy of tapentadol on the engagement of endogenous pathways	Procedure: - 3x OA trial: Individualized test temperature (42°C – 49°C)(5s) → +1°C (5s) → -1°C (20s) - 3x CPM trial: CS: (6°C - 18°C)(55s) TS (42°C – 49°C)(30s) - familiarization session - B: 32°C - OA → Lower part non-dominant arm. - CPM → CS: cold water immersion foot and lower leg, TS: thermal stimulus lower part non-dominant arm Devices: - 30mm x 30mm probe - NRS (CPM & OA) - eVAS (temperature set)	/	- significant CPM effect after placebo - significant CPM effect after tapentadol treatment - no effect of placebo and tapentadol treatment on OA response.	$P = 0.04$ $P < 0.01$ $P = 0.78$

Table 7. (cont.) *Evidence table.*

Study	Population	Study objective	Test protocol	Control protocol OA	Results	*P*-value/ Z-score
Ruscheweyh et al, 2014	- 30 patients after cerebellar infarction 21 m / 9 f 65.5 yrs ± 10.8 - 30 healthy controls 19 m / 11 f 66.0 yrs ± 11.4	Modulation of pain perception during placebo and OA in patients with cerebellar infarction	Procedure: - OA trial: individualized target temperature (5s) → +1°C (5s) → -1°C (20s) - constant trial: 35°C → individualized target temperature (Pain5/10 NRS) (30s) → 35°C - volar forearm ipsilateral to infarction (patients) or side determinded by randomization. - B: 35°C Devices: -25mm x 50 mm thermode - NRS(pain rating collected every 5s)	/	-OA was significantly larger in controls compared to patients - No significant main effect of anxiety and depression on OA	$P < 0.05$
Suzan et al, 2015	-30 patients with chronic lumbosacral radicular pain - 47.5 yrs ± 13.1	The effect of hydromorphone therapy on CPM and OA in neuropathic pain	Procedure: - OA trial: thermal stimulus ventral surface of the dominant forearm. 49°C (5s) → 50°C (5s) → 49°C (20s) → 32°C - CPM trial: CS: (12°C) (30s), TS: (47°C) (4s) - OA → thermal stimulus ventral surface of the dominant forearm. - CPM → CS: cold water immersion right hand, TS thermal stimulus left thenar eminence - B:32°C Devices: - 30 x 30mm thermode (CPM) - 16 x 16mm thermode (OA) - NRS (CPM) -coVAS (OA)	/	- oral hydromorphone treatment has no influence on CPM or OA	$P = 0.22$ resp. $P = 0.44$

B: Baseline temperature, ITT: individualized test temperature, VAS: Visual Analogue Scale, eVAS: electronic Visual Analogue Scale, COVAS: computerized Visual Analogue Scale, NRS: Numeric Pain Scale, PAG: periaqueductal gray, RVM: rostral ventromedial medulla, MCC: midcingulate cortex, pACC: pregenual anterior cingulate cortex, NMDA: N-methyl-D-aspartate, PA: Physical Activity

peripheral mechanisms trigger the OA paradigm by testing the occurrence of OA at the palm in comparison to the volar forearm, of which differences in nociceptor innervation is known. In addition, Martucci et al (22) investigated the influence of experimentally induced peripheral sensitization on OA. The involvement of the central nervous system in the mediation of OA was investigated by Yelle et al (16), using a paired stimulus paradigm. The latter authors (16) determined if OA could inhibit pain induced by primary afferent neurons in another region.

Three studies (28,32,34) used functional magnetic resonance imaging (fMRI) with a blood oxygenation level dependent (BOLD) signal to reveal activated brain regions during OA, while Hamaguchi et al (29) used a positron emission tomography (PET) scan to examine the same scope.

Four other studies (23,25,26,36) explored the central functioning of OA by examining the role of opioid receptors (using naloxone (23), tapentadol (26), hydromorphone treatment (36), and NMDA receptors (using ketamine (24)).

Additionally, Niesters et al (24,26), Honigman et al (30), Nahman-Averbuch et al (34), Naugle and Riley (35), and Suzan et al (36) compared the mechanism of OA to CPM.

Four articles investigated the influence of personal factors on OA magnitude. Three articles studied the influence of gender differences (25,30,31), 2 studies tried to objectify if the magnitude of OA differs between young and older healthy adults (25,31), and another study (35) examined the relation of physical activity with OA.

Methods OA

All thermal protocols started with a baseline temperature (T0) varying between 32°C and 35°C. Unpleasant stimuli (T1) varied between 45°C and 49°C, and painful stimuli (T2) varied

between 46°C and 50°C, for details see Table 7. Four studies (24,25,27,31) used individualized temperatures to induce OA, and the highest individualized temperature (perceived pain 15/20) provoked the largest OA-effect (27). To measure the OA effect; intensity of the maximum pain rating at T2 (dotted curve in Fig. 1a) and minimum pain rating at T3 are subtracted (ΔVAS = peak VAS during T2 – minimum VAS during T3). Seven studies that included a constant pain trial (16,17,27,28,30,32,34) found significant decreases in pain ratings during the OA protocol compared to constant painful stimulation.

The duration of stimulation varied among studies and appliance times of the different protocols are presented in Fig. 3. Martucci et al (22) and Yelle et al (32) are the only 2 studies with no constant time period of T1 and T2, and Naugle et al (31) was the only study applying a time period of 15 seconds for T1, which made stabilization of the perceived pain possible.

Underlying Mechanisms of OA

Temporal Processing

The studies of Yelle et al (16) and Martucci et al (23) examined whether OA functions as a temporal filtering mechanism, meaning that inhibitory mechanisms could increase the perceived temporal contrast and reduce post-stimulus responses. The occurrence of OA during different fall rates at both 48° and 50°C was reported (16), indicating no decrease of pain intensity in direct proportion to the stimulus fall rate. In accordance, Martucci et al (23) revealed significantly decreased pain ratings, for fall rates of -0.5°C/s as well as -5.0°C/s (using blocks of short-duration stimuli (49°C (4 – 6s)).

It is plausible that OA functions as temporal filtering mechanism, which increases the detectability of slow decreases in noxious stimulus intensity and induces post-stimulus inhibition (conclusion strength 2).

Brain Function

A change in activation induced by OA has been reported in multiple cortical (28,29,32,34) and subcortical regions (32,34), brain stem (28,29,32,34), and cerebellum (29,32,34).

Cortical brain structures – Three studies (28,32,34) reported less activation of contra- and ipsilateral primary somatosensory cortex (S1) during the painful stimulation in OA. Three studies (29,32,34) revealed more activation of the contralateral insula during OA compared to the constant pain trial. An increased OA induced activity of the dorsolateral prefrontal cortex (DLPC) was found by 2 studies (32,34). Dissimilar findings were reported concerning the mid-cingulate cortex (MCC) and anterior cingulate cortex (ACC), with an increased MCC and equally activated ACCs activity shown by Yelle et al (32) and decreased MCC and ACC activity compared with the constant trial reported by Derbyshire and Osborn (28). Respectively the first authors (32) also reported more deactivations of the ventral medial prefrontal cortex (VMPC) during OA than throughout the constant pain trial. The secondary somatosensory cortex (S2) was less activated during OA compared to constant pain (28).

Subcortical brain structures – Results regarding the thalamus are contrasting, with an increased activity reported by Yelle et al (32), and less activation of the thalamus during OA compared to a constant pain trial in Derbyshire and Osborn (28). The posterior aspect of the globus pallidus, which is in close proximity of the thalamus, also showed increased activity, although the rostral aspect displayed equal activation compared with the constant pain trial (32).

Brain stem – Three articles (28,29,32) revealed significantly greater activity in the periaqueductal grey (PAG) during OA compared to constant stimulation at the same point in time. However, Nahman-Averbuch et al (34) reported no differences in PAG activity. Nevertheless, the latter authors (34) did find a significant OA induced activation of the pons and medulla, which is supported by the results of Yelle et al (32).

Cerebellum – An OA induced increase of cerebral blood flow was objectified in the cerebellum by Hamaguchi et al (29) and supported by Yelle et al (32). However, Nahman-Averbuch et al (34) detected a significant decrease in cerebellar activation during OA.

It is proven that S1 exhibits reduced activity during OA (conclusion strength 1). Besides, it is plausible that the PAG, dorsolateral prefrontal cortex, insula, medulla, and pons are more activated during OA than during constant pain or rest (conclusion strength 2). There are indications for an OA induced increase in the cerebellum, although no full consensus exists (conclusion strength 3).

Spinal Mechanisms

Yelle et al (16) investigated the spatial stimulus interactions of OA, when assessed simultaneously at different sites. They reported lower pain intensities during OA trials both at proximal and distal probe (both on forearm 50 mm apart) compared to a constant painful stimulation (49°C) at both probes (P = 0.0042). Simi-

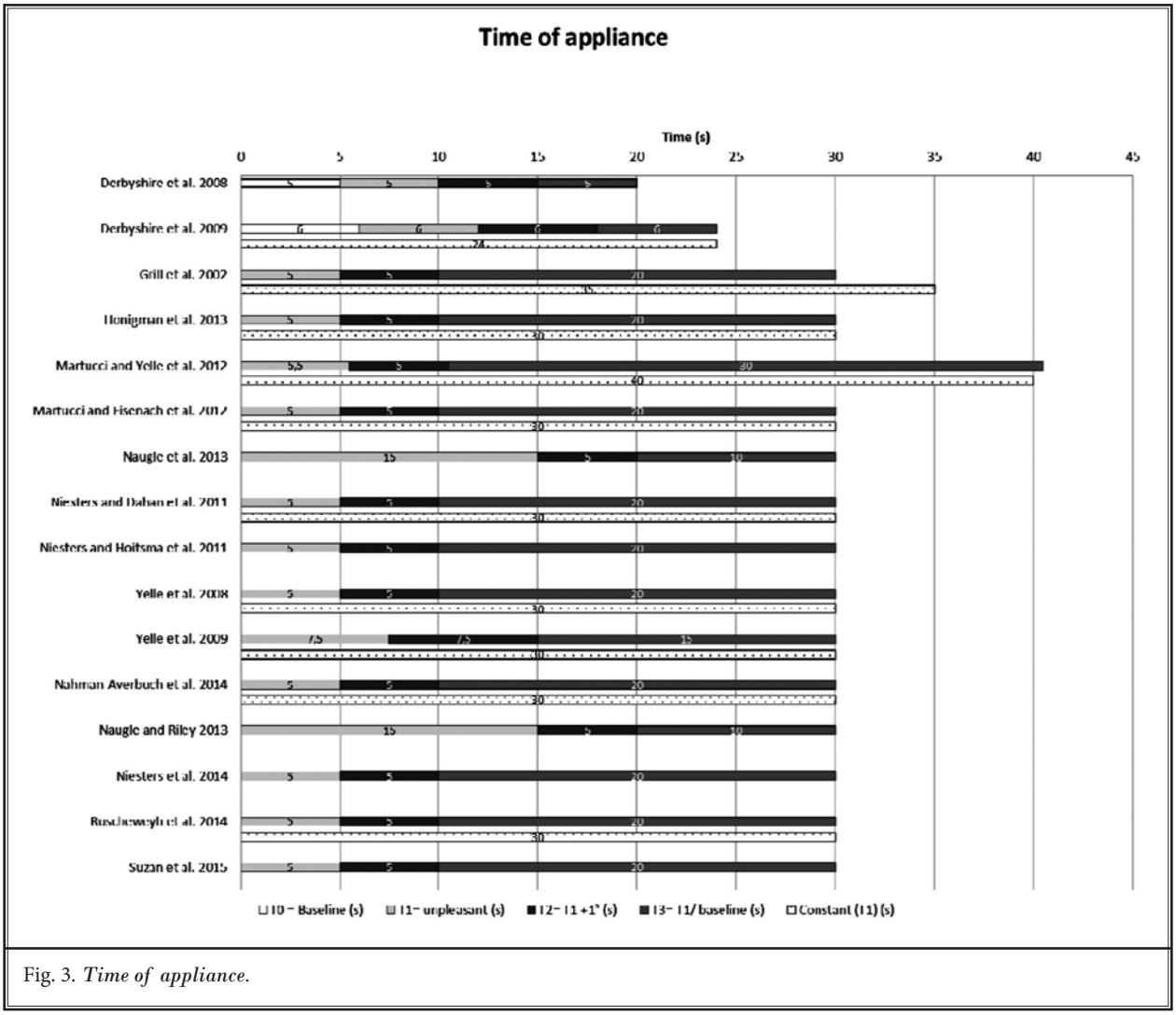

Fig. 3. *Time of appliance.*

lar findings were found when OA was induced at the proximal probe and painful stimulation (49°C) at the distal probe, compared to constant noxious stimulation (49°C) at the proximal as well as the distal probe (P = 0.0072). However, the exact opposite (noxious stimulation proximal and OA distal) did not result into significantly different pain intensities compared to painful stimulation (49°C) at both probes (P = 0.37). Moreover, potentiation of OA initiated by 2 probes was not significant (P = 0.34).

There are indications that OA is modulated by noxious stimulation within the same body region and that summation of OA-effect does not exist (conclusion strength 3).

Central Working Opioids and Neurotransmitters

Three studies (23,26,36) examined if OA is (in part) opioid-mediated, while another study (24) examined NMDA-mediated involvement.

There was no significant difference between the OA observed in healthy volunteers after infusion of the NMDA receptor antagonist ketamine (ΔVAS = 0.86 ± 0.06) and placebo infusion (ΔVAS = 0.91 ± 0.03) (24), indicating no NMDA-receptor involvement in OA. The study of Martucci et al (23) showed no reduction in the OA magnitude following remifentanil (= opioid analgesic) intake (P = 0.9310), representing no disruption of OA during a period of opioid-induced hyperalgesia. Ad-

ditionally, the OA response was not influenced by oral hydromorphone (= opioid analgesic) treatment in the study of Suzan et al (36) (P = 0.44). Naloxone (= opioid antagonist) (P = 0.3211) did likewise not influence the OA magnitude, which indicates no opioid contribution as well (23). This is supported by the results of Niesters et al (26), which showed that tapentadol (= opioid agonist and norepinephrine reuptake inhibitor) treatment had no effect (P = 0.78) on OA magnitude.

It is proven that OA is not opioid dependent (conclusion strength 1). Besides, there are indications that OA is not NMDA-receptor dependent either (conclusion strength 3).

Peripheral Mechanisms

Two studies (22,31) investigated predominantly peripheral mechanisms during OA.

Martucci et al (22) suggested that OA would be disrupted during a state of experimentally induced sensitization. Sensitization at the forearm was induced by applying capsaicin cream followed by a heat stimulus. Results showed no significant alteration in OA magnitude (P = 0.56). To determine the influence of afferent fibers on OA effect, Naugle et al (31) analyzed distinct afferent fibers by positioning a probe on the palm and a separate probe on the volar forearm. Results indicated only OA effects at the forearm.

There are indications that OA is not disrupted by experimentally induced sensitization (conclusion strength 3), however, peripheral mechanisms might be involved in initiating OA (conclusion strength 3).

Duration

Two studies (16,17) investigated the time-course of OA and revealed that minimum pain intensity ratings during OA were significantly lower than minimum pain ratings evoked by constant thermal stimulation at T1 (P < 0.01) in the 20 seconds following the 1°C decrease. This analgesia lasted approximately 15 seconds.

It is plausible that the analgesia evoked by OA lasts 15 seconds (conclusion strength 2).

Individual Factors Influencing OA

Gender

Four studies investigated the effect of gender on OA efficacy (24,25,30,31). Two articles (25,30) reported significantly higher OA magnitudes in men compared to women. The study of Honigman et al (30) additionally exposed a negative correlation between pain sensitivity and OA efficacy which was detected in women (r = 0.53, P = 0.04), though not in men (P = 0.56). The gender effect in the study of Niesters et al (25) was age-dependent, as no gender-differences were observed in young (6 – 19 years) volunteers (P = 0.185), while in older adults (20 – 80 years) significant gender differences were exposed (P = 0.002), with men predisposing for better OA.

Two other studies (24,31) could not demonstrate significant gender differences in OA magnitude.

Evidence for gender differences in OA magnitudes is conflicting (conclusion strength 3).

Age

Two articles (25,31) reported differences in OA magnitude between younger and older adults. Niesters et al (25) showed a trend towards reduced OA with increasing age, however only border significant differences between the age cohorts could be objectified (P = 0.054). This was supported by Naugle et al (31) who actually revealed significant differences in OA magnitude, with older adults exhibiting reduced OA magnitudes at the forearm, compared to the younger group (P = 0.048). However, at palm side equal responses were reported.

There are indications for decreasing OA magnitudes with aging (conclusion strength 3).

Physical Activity

Only one study evaluated the influence of physical activity on OA magnitude (35). Although a positive effect of more vigorous and total physical activity on CPM-effect was found, no outcome on the International Physical Activity Questionnaire predicted OA magnitude.

There are indications for no predictive value of physical activity level to OA efficacy, however evidence is limited (conclusion strength 3).

OA in Patients

In neuropathic patients OA effects seemed to be delayed and smaller compared to healthy controls (P < 0.001), even though the individual test temperatures and mean peak VAS did not significantly differ between patients and healthy controls (respectively P = 0.91 and P = 0.44) (25). Following ketamine and morphine treatment, pain scores were significantly lower in neuropathic pain patients but no effect on OA was detected (25). Also in patients with diabetic polyneuropathy (26), chronic neuropathic (radicular) pain (36), and patients who suffered from cerebellar infarction 1 to 11 years ago (33), no clear OA-effect could be objectified.

Decreased OA-effects in neuropathic patients are proven (conclusion strength 1). The observations from patients with cerebellar infarction, together with brain imaging studies, give indications for involvement of the cerebellum in OA (conclusion strength 3).

Differences between OA and CPM

Four articles (24,30,34,35) revealed different mechanistic properties of endogenous analgesia through CPM versus OA in healthy people.

The study of Nahman-Averbuch et al (34) exhibited a greater reduction of activity in brain regions associated with afferent nociceptive processing during CPM than during OA, although S1 displayed greater deactivation in OA. Subsequently, modulation of nociceptive processing was more activated during OA. In multiple levels of the brain stem, CPM induced reduced activity, while OA produced increases in activity. For more detailed information see Nahman-Averbuch et al (34).

Moreover, Niesters et al (24) revealed no change in OA magnitude after ketamine administration, but a reduced CPM response was observed, as pain responses were significantly higher ($P < 0.01$). Additionally, one study in diabetic polyneuropathy patients (26) revealed a higher CPM efficacy following tapentadol treatment ($P < 0.001$) while OA magnitude was not altered ($P = 0.78$). However, hydromorphone did not significantly influence CPM ($P = 0.22$) or OA ($P = 0.44$) in neuropathic patients (36).

Interestingly, Honigman et al (30) revealed an additive effect of CPM on OA in men, as an OA+CPM condition showed significantly greater pain reduction than an OA standalone condition ($P = 0.003$) and a trend towards additive effects of OA on the standalone condition of CPM in men ($P = 0.07$).

Finally, one study (35) examined possible differences in individual factors influencing the magnitude of OA and CPM. Self-reported total and vigorous activity in healthy people did predict CPM-effect, while no correlation with OA-effect could be detected.

CPM and OA plausibly rely on different mechanisms (conclusion strength 2) and are possibly influenced by different personal factors such as daily activity levels (conclusion strength 3). Nonetheless, indications suggest that both may influence one another (conclusion strength 3).

Discussion

This systematic review was developed to provide an overview of the current knowledge regarding OA, more specifically to objectify the methods used in OA assessment, unravel the mechanisms triggered by OA, map the personal factors that influence OA (assessment), represent OA in patients, and to compare OA with CPM.

Methods OA

The present review objectifies OA as a pain protocol that is increasingly used in assessment to measure endogenous pain inhibition. The included OA protocols are reasonably similar, which makes comparison of the study protocols possible. Sixteen out of 17 studies used quantitative sensory testing (QST) with hot temperature to provoke OA-effects. However, only 4 studies (24,25,27,31) used individualized temperatures to provoke OA. An individually determined temperature (perceived pain 15/20) seems to induce greater OA-effects compared to lower temperatures, however evidence is preliminary. Additionally, OA-effects are possibly dependent on the assessment site (31), though further research is necessary. Since no gold standard exists, small differences in protocols are present. For instance, 7 studies (24-26,29,31,35,36) lacked additionally assessed constant trials. These trials are recommended to calculate effect sizes of the OA magnitude since part of the OA-effect can be ascribed to adaptation (27). For this reason, future OA assessment should include constant trials in their protocol as it was originally described by Grill and Coghill (17).

Underlying Mechanisms of OA

OA probably functions as a temporal filtering mechanism, which enhances the detectability of noxious stimulation and induces post-stimulus inhibition (16,23). This post-stimulus inhibition appears to last for 15 seconds (16,17) which is important for the development of OA assessment protocols. New protocols should also take the spatial interactions that possibly influence OA into account: for example; the asymmetric spatial interactions found in the study of Yelle et al (16) that substantiates the modulation of OA by other noxious stimulation at the same body region. Since summation of OA was not objectified in this latter study, central mechanisms at the spinal level as well as descending inhibitory tracts seem to be involved in OA (16).

The large involvement of central mechanisms in OA is clearly established by brain imaging studies. These studies demonstrate reduced activity of the S1 during OA (28,32,34) that goes along with increased activation during OA compared to constant pain stimuli

in brain regions associated with descending pain inhibitory pathways; PAG (28,29,32), dorsolateral prefrontal cortex (32,34), insula (29,32,34), medulla (32,34), pons (32,34), and cerebellum (29,32,33).

Because of the partial overlap with brain activity in the regions associated with placebo (expectation) (37), distraction (38), and mindfulness (39), cognitive processes may be involved in OA as well (34). Moreover, Loggia et al (40) revealed that lower pain-anticipatory lateral prefrontal activity contributes to hyperalgesia induced by negative cognitions (catastrophizing) in fibromyalgia patients. Additionally, impaired OA-effects as well as reduced placebo analgesia are exhibited in patients with cerebellar infarction (33). Although the exact contribution of cognition in OA-magnitude needs further study, cognitive involvement in OA-effect is conceivable.

Individual Factors Influencing OA

Studies examining the influence of personal factors on OA are scarce. Gender studies point to greater OA magnitudes in men, which is in accordance with CPM-effects (21), however, no full consensus exists (24,25,30,31). In addition, there are indications for decreased OA-effects with aging (25,31), but evidence is limited. The age-related effect of the decrease in β-endorphins at rest and a smaller release of β-endorphins during painful stimulation are possible explanations for this decrease (41). Thus far, only one study (35) investigated the influence of physical activity and did not find a relation. Nevertheless, evidence indicates that physical activity considerably improves cognitions and efficient brain functions (42), and as described above, these may be involved in generating the OA phenomenon. Subsequently, improved OA magnitudes with higher physical activity levels could be expected and needs further exploration. As OA seems to be more brain derived and the influence of anticipation on CPM is frequently reported (43-45), further research about these factors in OA is necessary. The same applies for other modifiable factors linked to pain and assessment (attention, expectations, catastrophizing, anxiety, etc.).

Non-modifiable personal factors like genetics (46,47) and hormonal factors (48,49) have been reported to influence CPM, and are possibly also influencing OA, but studies are lacking.

OA in Patients

Current literature does provide indications for decreased OA-effects in neuropathic patients (25,26,33,36). As effective descending inhibitory pathways protect progression of chronic neuropathy and improves quality of life (50), research regarding neuropeptides etc. involved in these pathways is necessary.

As mentioned earlier, impaired endogenous pain inhibition in patients with central sensitization, assessed by CPM, is frequently reported (2,5,9,12). As OA probably evaluates more brain derived pain modulation compared to CPM, impaired OA is also assumed in these patients. This is supported by a very recent study of Oudejans et al (51) that displayed reduced OA-effects in patients with fibromyalgia. These authors additionally demonstrated lower pain perception and pain tolerance thresholds in patients with reduced OA. Therefore, it can be hypothesized that hyperexcitability to heat pain plays a role in the loss of OA-effect, however, more research is necessary. Additionally, whether the loss in OA-effect in these patients with central sensitization is more peripheral, central, or a combination, should be further investigated.

Differences Between OA and CPM

The OA mechanism differs in all probability from the CPM phenomenon (24,30,34,35). Next to the above mentioned differences between OA and CPM, aberrant brain activation is an important feature; for example, activity reductions in brain regions related to afferent nociceptive processing observed during CPM and increased activations in circuitry subserving pain modulation through OA. These findings probably reflect more brain derived pain modulation during OA as compared to CPM (34). In line with this, it is important to note that CPM is the psychophysical spatial assessment tool to measure multiple inhibitory mechanisms, such as DNIC (spinal-medullary-spinal loop), heterotopic inhibition mediated by local circuits at the spinal level, and heterotopic noxious conditioning stimulation (supraspinal top down pathways) (52,53). As for OA, current evidence supports the activation of supraspinal inhibitory top-down pathways and only indications for mediation at the spinal level exists.

Concomitant are the diverse effects of medication on the different pain assessments. Opioids and NMDA-receptors do not seem involved in OA (23,26,36), however, results regarding the involvement of opioids in CPM are contradictory (26,36). Subsequently, temporal summation appears to be more opioid dependent compared to CPM (54). Therefore, the opioid induced analgesic effects may be more applicable at spinal than supraspinal levels (54). Hence, to evaluate the opioid-

mediated descending pathways, OA and CPM assessment should feasibly be accompanied by other tools.

Preliminary evidence objectified the modulation of OA by other noxious stimulation (16). This is somewhat contrasting to the indications that OA is not disrupted by capsaicin-induced tissue sensitization at the assessment site (22), although probably different pathways are involved. Regarding capsaicin-induced sensitization, one should note that despite predominantly evaluating peripheral mechanisms, the involvement of central components is conceivable (55). To the best of our knowledge, only the study of Oono et al (56) investigated the effect of induced acute pain on CPM. These authors reported no influence of experimentally induced noxious stimulation of the temporal mandibular joint on CPM-effect. Albeit, evidence is preliminary and no consensus exists, these studies give implications for aberrant OA and normal CPM effects in patients with already clinical (sub)acute pain and no influence of assessment site tissue sensitization in OA. Currently, studies only investigated CPM-effects in patients with acute postoperative pain. The multiple aspects associated with postoperative pain (e.g., medication, immobilization, psychological factors, etc.) may shadow pure CPM-effects (15). Consequently, further research into OA and CPM in patients with acute pain and patients with central sensitization are recommended.

Hence, CPM and OA appear to rely on different mechanisms. Nevertheless, further research is warranted to disentangle OA and CPM mechanisms and to discover their specific pathways.

Limitations and Suggestions

Five articles (16,17,24,28,34) used a sample size of less than 15 participants, probably presuming a power that is insufficient to make firm conclusions. Besides, 2 articles scored below 50% on the risk of bias checklist (25,28). All RCTs scored one point for blinding the patient, because self-reported pain is proven to be a valid and reliable assessment method (57) and is the only suitable option in the OA protocol. Nonetheless, after receiving the infusion (naloxone, tapentadol, remifentanil, ketamine), different side effects occurred (nausea, dizziness, vomiting) (23,24,26). Therefore, it is possible that experiencing side effects following the experimental infusion and not following the control infusion could have compromised blinding of the participants regarding the experimental/control intervention and thus influenced their self-reported pain intensity due to certain expectations. It is recommended for future studies to give a clear description regarding the blinding of therapists, assessors, and participants.

Finally, search strategy was taken wide and no predefined directions were made, because research into OA is currently limited. Therefore a large variety of research perspectives (e.g., inventorying different assessment protocols, influencing factors, central and peripheral mechanisms, etc.) of OA were included in this review. The methodological differences accompanied by the different perspectives of these studies might have influenced the outcomes and therefore could have influenced conclusions made by the present review.

Clinical Implications

Clinical applications of OA are currently not clear due to limited available research. Nevertheless, future OA studies may improve the understanding of (the pathophysiology of) various chronic pain conditions. Consequently, new treatments can be developed based on a new understanding generated from these research projects. Based on the preliminary evidence regarding the overlap of brain activity in regions associated with cognitive processes, future research should focus more on these mechanisms. For instance, there might be a possibility to potentiate OA by attention and expectations (27). Besides the fact that OA can serve as an assessment tool for the efficacy of endogenous pain inhibition, further research is necessary to examine how OA can be of clinical relevance, e.g., in the assessment of the relation between cognitions and pain and the effect of more cognition-targeted therapies.

Conclusion

The findings of this review objectify OA as a temporal sharpening mechanism, which can function as a non-opioid mediated assessment tool for endogenous pain inhibition. OA activates brain regions such as PAG, dorsolateral prefrontal cortex, insula, medulla, pons, and cerebellum, indicating strong brain derived pain modulation. Hence, further research of OA as an assessment tool in e.g., the evaluation of cognition-targeted therapies is warranted. Besides, evidence regarding OA in (sub)acute pain and central sensitization patients, and the influence of personal factors on OA is currently scarce. That reinforces the need for further research exploring OA, also prospectively, to support treatment.

Authors Contributions

LH was involved in establishing the method, performed the analysis, and wrote the paper. PC assisted

with analysis and writing of the paper. JVO was involved in establishing the method, and assisted with analysis and writing of the paper. EV screened the search results of the databases for eligibility, and assisted with writing the paper. EB screened the search results of the databases for eligibility, and assisted with analyses. MM was involved in establishing the method, assisted with analyses and writing the paper.

Conflicts of Interest

The authors have no conflicts of interest to declare. Level of funding 0.

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