COGNITIVE IMPAIRMENT ASSOCIATED WTH CHRONIC PAIN

THE EXTENT OF THE NEUROCOGNITIVE IMPAIRMENT ASSOCIATED WITH CHRONIC PAIN ON THE NEUROPSYCHOLOGICAL TEST PERFORMANCE; META-ANALYSIS AND LITERATURE REVIEW

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Abstract:

Introduction:
Cognitive complaints are often reported by patients who also describe chronic pain. Reviews suggest chronic pain is likely to be associated with weaknesses, relative to control groups, in at least some cognitive functions including processing speed, attention, and possibly working memory, but differences between studies obscure the size of effects.

Objective:
This study provided a quantitative analysis of the magnitude of the association between chronic pain and neurocognitive test performances. A brief literature review is also done to focus on the functional brain changes associated with the chronic pain.

Methods:
Meta-analysis was performed using the Cochrane, PRISMA guidelines. The analysis included published experimental design and the tests were studied at least 3 times, by different researchers, and the outcomes were combined within the same cognitive test. Tests were excluded when heterogeneity of variance exceeded $I^2 = 0.60$. Pain subgroups were combined.

Results:
23 studies met criteria and involved heterogeneous pain populations, or subgroups including back pain, whiplash, and fibromyalgia. Seven tests had sufficient variance homogeneity. Effects sizes (- ve = chronic pain relative weakness) were: Tests measuring the attention such as PASAT and TEA, working memory (WAIS- digit span), executive functions such as Stroop test, TMT showed significant weaker performance on the tests performance, whereas performance on the test of visuospatial abilities such as ROCF and Corsi block test and WCST test, did not showed significant association.

Conclusions:
Chronic pain was associated with statistically significant performance reductions. The pattern suggests that chronic pain is associated with poorer performance in at least some tasks requiring processing speed, attention, working memory and learning. Differences between pain and control groups ranged from about 1/3 standard deviation to just under a full standard deviation. Too little research is available on non-verbal memory and executive functions in chronic pain.

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Contents

Chapter 1: Study background

Chronic pain as a societal, productivity and emotional burden:

A significant patient population suffers with chronic pain and related problems; however half of them do not receive adequate pain management (van Dijk et al 2009; Breivik et al 2006). Loss of cognitive function is likely to impact the execution of daily tasks and, therefore, negatively affect the individual's relationships, capacity to work, mood and quality of life, which can lead to functional disability (Lew et al 2006; Lew et al 2009; Hart et al 2000). In clinical settings chronic pain is often overlooked when assessing and treating the patients with neuro-cognitive and psychological impairment. The increasing prevalence of pain-related illnesses has high economic and psychological consequences.

Chronic pain is a widely prevalent, but under studied, social and clinical entity. These individuals consume an enormous amount of resources (Boersma et al 2005). The prevalence of chronic pain increases with age and females have increased propensity for the development of chronic pain. However, chronic pain is not restricted to only older age groups; a significant proportion of young adults and teenagers also suffer from chronic pain conditions such as headaches .Chronic pain and associated problems represent a significant economic burden for patients, healthcare systems and societies. **Table #1** show the societal burden associated with the levels of chronic pain in different countries.

Blyth et al 2001 conducted a phone interview of the Australian general population and reported that chronic pain was significantly associated with older age, female gender, lower level of completed education, and lack of private health insurance. In addition, they reported that chronic pain was strongly associated with receiving a disability benefit, unemployment, poor self-rated health and a high level of psychological distress. Chronic pain is significantly associated with interference with routine work related activities; with younger patients most likely to report interference due to pain, affecting 84.3% of females and 75.9% of males aged between sixteen and 28 years with chronic pain.

Breivik et al 2006 concluded that 19% of adult Europeans suffer from chronic pain, affecting the quality of their social and working lives. Breivik et al 2006 conducted telephone survey in 15 European countries and in Israel and reported 19% of the respondents had suffered pain in the last 6 months and several times during the week prior to the interview. 59% had suffered with pain for 2 to 15 years and 21% had been diagnosed with depression because of their pain. Of the total, 61% were less able or unable to work outside their homes, 19% had lost their jobs and 13% had changed jobs because of their pain. 60% of the respondents had visited their doctor about their pain 2–9 times over the previous six months; however, only 2% were currently being treated by a pain management specialist. In the survey, one-third of the chronic pain sufferers were

not treated. These patients had to bear significant treatment burdens such as massage therapy (30%), physical therapy (21%), and acupuncture (13%). Half of the chronic pain patients were taking non-prescription analgesics; over the counter (OTC) NSAIDs (55%), paracetamol (43%) and weak opioids (13%). Two-thirds took prescription medicines, 44% took NSAIDs, 23% took weak opioids, 18% took paracetamol, 36% took COX-2 inhibitors and 5% took strong opioids. Forty percent of the chronic pain patients had inadequate management of their pain.

Similar data is reported in USA. Gore et al 2012 and Johannes et al 2010 reported data collected from the general public from Massachusetts and New York states respectively. Gore et al 2012 reported chronic low back pain was more prevalent in females and over all chronic back pain patients had significant co morbidities as compared to general population, particularly depression (13.0% vs. 6.1%), anxiety (8.0% vs. 3.4%), and sleep disorders (10.0% vs. 3.4%), increased pain related pharmacotherapy opioids (37.0% vs. 14.8%), non-steroidal anti-inflammatory drugs (26.2% vs. 9.6%), and tramadol (8.2% vs. 1.2%). 36.3% of patients received combination therapy or adjunctive medications to treat the associated co-morbidities such as depression, anxiety, and insomnia in chronic low back pain patients. Total direct medical costs were estimated at $8386 to$17,507 in the CLBP group and $3607 to $10,845 in the control group. On the other hand, Johannes 2010 reported that the chronic pain prevalent rate was 30.7%. As reported previously, females had higher prevalence (34.3%) than males (26.7%). Half of the respondents with chronic pain had experienced daily pain in the previous three months. Chronic pain was strongly associated with low household income and unemployment as significant socioeconomic correlates of chronic pain.

Two large Canadian surveys, Gilmour et al2003 (**Table# 2**) and Ramage Morin et al 2005, reported the effects of chronic pain in the general population. Gilmour et al2003 reported the impact of several chronic pain conditions on general Canadian populations. For this thesis, I only extracted the data related to chronic pain conditions.

Ramage Morin et al 2005, reported prevalence of chronic pain among seniors living in private households and in long term health care institutions. Data from Canada's 1994/1995 through 2002/2003 National Population Health Survey (NPHS) and 2005 Canadian Community Health Survey (CCHS) were collected. According to the report, thirty-eight percent of institutionalized seniors experienced pain on a regular basis, as compared with 27% of seniors living in private households. In both populations, rates were higher for women than men (**Table #3**). According to the Health Canada report, Reitsma et al 2011 (**Table# 4**), chronic pain prevalence had increased in general Canadian population between 1994 and 2008.

Table #5 is the facts sheet published in 2013 in Canada Pain Society. The key features of this report are illustrated in the table. Jakobsson et al 2010 reported that half of the total pain population do not have the cause or diagnosis of their pain and 21% of the total pain population do not receive adequate pain management (Jakobsson et al

2010). 62% of the chronic pain patients in an outpatient chronic pain program report moderate to severe problems with at least 1 out of 5 possible cognitive areas (Roth et al 2005). About 40 to 50% of chronic pain patients have associated depression. Schopflocher et al 2011 reported chronic pain prevalence in different Canadian provinces. This data excludes the territories and Canadian Armed Forces (**Table # 6**)

Philips et al 2006 reported socioeconomic burden across different countries. Over 100 million Europeans and one in four people worldwide have chronic musculoskeletal pain (Philips et al 2006) (**Table # 7)**.

Chronic pain and chronicity:

In my opinion, it is empirical to study the effect of chronicity and individual thought process that result in the pain related disability. Researchers have studied the chronicity and physical pain related disability; however, very few have reported the effect of pain chronicity and cognitive functions. Gatchel et al 1999 reported several cognitive and psychological variables that play a role in the development of the pain-related disability; whereas Verdejo-Garcia et al 2009 reported pain chronicity is inversely related to cognitive deficits.

Pain chronicity is defined as the length of time the individual had suffered from debilitating pain and related disabilities (Pincus et al 2002; Sullivan et al 2002). Three stages of chronicity, such as threat, rumination, and helplessness, have been reported that moderate the relationship between the pain catastrophizing and chronicity (Sullivan et al 2002; Rodero et al 2010). Researchers have reported different variables responsible for the chronicity and vulnerability to the disability (Wang et al 2009, Sullivan et al 2002, Boersma et al 2005; Pincus et al 2002); however, the literature focusing on the contextual factors associated with persistent pain and pain-related disability vulnerability is sparse. The common factors in the literatures are age, gender, psychological factors, fear or avoidance, catastrophizing, self-efficacy and personal control (Vlaeyen et al 2000, Sullivan et al 2001, Boersma et al 2005).

The important underlying mechanism attributed to chronicity is pain catastrophe. Pain catastrophizing represents a heightened pain, vulnerability and disability associated with pain (Sullivan et al 2001). Pain catastrophizing thoughts lead to pain-related fear (Wang et al 2009). Catastrophizing and fear thoughts have been reported to be associated with increased prevalence of chronic back pain one year after acute low back injury (Swinkels-Meewisse et al 2006).Rumination and helplessness predict pain-related disability for individuals who have pain for two to four and more than four years, respectively (Sullivan et al 2002, Rodero et al 2010). Sullivan et al 2002 reported that rumination predicts pain-related disability after pain is controlled, thus is independent of the pain. Sullivan et al 2002 and Boersma et al 2005 reported that chronicity beyond one year is a key factor in the establishment of the chronic pain; however pain less than two years duration is less catastrophizing.

Pain-related fear over predicts the severity of pain with subsequent avoidance behaviour and delayed pain resolution (Wang et al 2009). However, Boersma et al 2005 reported that fear of movement is not a significant predictor of chronicity until after one year of pain duration. Fear and anxiety modulates pain through the medial prefrontal region, ventral lateral frontal region, and cingulate cortex of the brain, whichare associated with monitoring and evaluation of affective responses.

Depression and anxiety are commonly associated variables reported in post surgical patients (Brander et al 2003). Regardless of the stage of the chronicity,

depression is negatively associated with pain related disability and chronicity (Boersma et al 2005). Between 30% and 65% of patients with chronic pain have co-morbid depression, however depressed and anxious patients are two to five times more prone to develop chronic pain in the long run (Wang et al 2009).

Other important variables associated with chronicity and pain related disabilities are social and environmental factors, which impact the psychological vulnerability (Sullivan et al 2002). Magnification has not emerged as a major predictor of pain-related disability; however magnification may exert its effects indirectly through heightening the pain experience (Sullivan et al 2002).

Post operative acute pain and factors leading transition to chronic pain:

It is important to understand the transition of acute pain to chronic pain. Acute pain usually follows any trauma or tissue insult. A surgical model was selected, as acute pain following surgery is predictable and is a physiological response to tissue damage. Patients are prepared for some degree of pain or discomfort but expect that the pain will pass. However, 2–10% of surgical patients develop chronic post surgical pain, which is a persistent or intermittent pain of varying severity at one year postoperatively (Kehlet et al 2006).

Chronic post surgical pain (CPSP) develops within two to three months of the surgery and when all other organic causes of the pain are ruled out (Macrae WA et al 2008, Katz et al 2009). Events following the acute injury are important to the development of chronic pain. The aim of this section is to critically examine the factors that are associated with the development of chronic postsurgical pain or that lead to chronicity. Chronic post surgical pain (CPSP) is reported in patients undergoing common procedures such as hernia repair, breast and thoracic surgery, leg amputation, and coronary artery bypass surgery (Bruce et al 2011).Lynch et al 1998 reported that in patients undergoing elective non-cardiac surgeries, particularly total hip replacement surgery, pain was an independent risk factor for the development of delirium in patients aged 50–80 years. Heyer et al 2000 demonstrated that postoperative pain predicted impaired neuropsychological performance in postoperative spinal surgery patients over the age of 60, but that duration of surgery, dose or type of anaesthetic did not.

Prevalence:

Crombie et al 1998; Hayes et al 2002 and Brown et al 2004 reported acute neuropathic pain in up to 3% of post surgical patients and 56% of these patients continued to have pain on one year follow up, whereas 10% of these patients had developed severe, intractable chronic postsurgical pain. Other studies reported 10% to 30% of surgical patients had developed persistent pain at one year postoperative follow up (Alfieri et al 2006, Macrae et al 2008). Most authors have focused on common elective surgical procedures such as hernia repairs, mastectomy, orthopaedic and cardiac and thoracic surgeries.

Generally, post operative pain patients are followed until one year after surgery but follow up beyond one year is not common. Based on the data reported, the chronic pain after surgery could be specific to surgery type: 10–15% of the patients developed chronic pain following modified radical mastectomy (Jung et al 2005); 61–70% thoracotomy patients developed chronic pain; 60% of amputees have phantom limb pain (PLP) and 21–57% have residual stump pain (Perkins et al 2000; Alfieri et al 2006, Macrae et al 2008);6% of patients developed persistent testicular pain after hernia repair

(Aasvang E et al 2005); and up to 56% patients develop CPSP after gallbladder surgery (Perkins et al 2000).

Risk factors:

Factors leading to post surgical chronic pain, are sub divided into pre-operative, intra-operative and post operative factors. Other authors have sub divided the risk factors into patients factors; surgical factors; psychosocial; and social and environmental factors.

Pre-operative factors:

Pre-existing pain in patients undergoing breast surgery (Tasmuth et al 1996), thoracotomy (Searle et al 2010), hernia repair (Liem et al 2003), amputation and phantom limb pain (Perkins et al 2000), anterior cervical decompression and fusion (Peolsson et al 2003) is reported as an independent risk factor in the acute postoperative period (Caumo W et al 2002).

Patients with prolonged or chronic opioid intake before surgery are prone to experience CPSP due to opioid induced hyperalgesia (Lamacraft 2012). Similarly, preoperative depression and anxiety increases the incidence of chronic post operative pain (Perkins et al 2000).

Intraoperative Factors:

The type of surgery, the use of a prosthesis, surgical clips, post operative radiation and chemotherapy, increases the risk of CPSP in radical mastectomy patients (Perkins et al 2000). Patients undergoing hernia repair with mesh and pericostal and intracostal stitches have increased risk of chronic pain development (Katz et al 2009). Other important intraoperative risk factors are: chronic inflammation due to non-absorbable material such as staples, sternal bone wires, neuroma formation with entrapment of fibres in scar tissue (Bruce et al 2011), and duration of anaesthesia and surgery (Shipton et al 2005).

Postoperative Factors:

Chemotherapy and radiotherapy following breast cancer, phantom limb pain (Searle et al 2010, Perkins 2000), poorly controlled postoperative pain (Perkins et al 2000) and reoperations (Sondenna et al 2001) are post operative risk factors for the development of persistent CPSP.

Psychosocial factors

Pre-operative psychological factors such as anxiety and catastrophizing play a significant role in the transition of acute pain to chronic problems (Linton et al 2000).

Catastrophizing

Fear-avoidance, negative thoughts or exaggerated negative 'mental set' are associated with increased incidence of CPSP (Katz et al 2009).

Chronic postsurgical pain & post-traumatic stress disorder

The exact association between chronic pain and PTSD is unknown. However, there exists an overlap of symptoms between the two conditions, such as anxiety, hyper arousal or sleep disruption, attention compromise, avoidant behavior, and elevated somatic focus (Asmundson et al 2002).

Increased prevalence of chronic pain and psychological impairments has been reported in Holocaust survivors (Yaari et al 1999) and veterans returning from Iraq and Afghanistan (Lew et al 2009). Co-prevalence between chronic pain and PTSD in two post surgical patients following awareness under anesthesia (Solomon et al 2004), lateral thoracotomy (Katz et al 1997), and fear of pain and recurrence in cancer patients (Katz et al 1997) have been reported.

Genetic susceptibility

Genetic variability such as catecho-O-methyl-transferase enzyme (COMT) polymorphisms in the dorsal root ganglion correlates with the developing chronic temporo-mandibular joint pain and persistent pain after lumbar disectomy (Kehlet et al 2006 and Searle et al 2010).

Age and gender:

Women and young adults have increased prevalence of chronic post surgical pain (Lamacraft 2012).

Empathetic responses:

The response of significant others in response to patient's complaints of pain or grimaces are reported to contribute to pain-related disability (Katz et al 2009).

Other factors:

Inactivity; time off work after the surgery; education of less than ten years, and divorced or separated persons all had 1.5 higher odds of chronic pain (Eriksen et al 2003, Shipton et al 2005).

Pathogenesis:

The exact mechanism of acute surgical pain transitioning to chronic pain is not known. It is speculated that tissue and nerve damage in surgery results in inflammation, which increases the spontaneous discharge of nociceptors leading to primary hyperalgesia and peripheral and central sensitization, and increased motor and sympathetic outputs (Katz 2009). Central sensitization leads to repetitive ectopic neural activity, altered dorsal horn neuronal activity and amplification of sensory flow; this can lead to persistent nervous system changes (Bruce et al 2011).

Imbalance between the excitatory and inhibitory neurotransmitters such as postsynaptic NMDA receptors and GABA and glycine leads to the destruction and loss of disinhibition of pain pathways (Kehlet et al 2006). Activation of protein kinase C, tumor necrosis factor (TNF) α and altered sodium conductance contributes to spontaneous pain (Lai et al 2004). The nociceptive impulses induce changes in the brainstem and cerebral cortex connectivity (Schloz et al 2005).

Animal Model of chronic pain and cognitive dysfunction:

For pre-clinical literature, I collected studies using the Ovid Med line, Mc Master Data base. All the studies published between 1946 and 2013 were reviewed. The literature search strategy is given in **Table # 8**.

Summary of the important published literature:

The following studies (**Table # 9)**, were reviewed based on the literature strategy (see **Table #8**). Pre-clinical studies provide an opportunity to understand the association between chronic pain and cognitive dysfunctions. The pre-clinical pain model is an under studied area, with few published studies to correlate the pain-related cognitive impairment. In pre-clinical studies, the pain related cognitive activities are mostly dependent on the locomotor and appetite activities of the animals. In the above studies, Cain et al 1997; Lindner et al 1999; Leite-Almeida et al 2009 reported impaired motor functions in neuropathy pain models; whereas Hu et al 2010; Leite-Almeida et al 2009; Suzuki et al 2007, studied impaired swim time. Boyette- Davis et al 2008, Cain et al 1997 and Linder et al 1999, found attention learning and memory deficits on delayed lever press in rats in response to operant nose poke task and Freund's adjuvant pain. Millecamps et al 2004 reported decrease in attention on novel object recognition in response to visceral pain. In Millecamps et al 2008, Boyette- Davis et al 2008 and Pais-Vieira et al 2009(a) studies, rats with pain spent less time exploring the new object as compared to the control rats. Pais-Vieria et al 2009(a) also reported a decreased in correct nose pokes but an increase in the number of omissions.

Pais-Vieria et al 2009(b) and Ji et al 2010 reported that rats had impaired emotional decision making on rodent gambling task such as infrequent rewards on high risk lever as compared to alternative lever. Hu et al 2010 reported spatial learning and memory impairments in rats in response to L5 spinal nerve transaction. Impairments in mental flexibility and spatial reversal task, which are analogous to executive functions in clinical studies, were reported in rats secondary to neuropathic pain (Leite-Almeida et al 2009). However no strong association between pain and cognitive function was reported in Suzuki et al 2007 experiment. Kodama et al 2011 reported impaired recognition memory in mice suffering with spinal pain. Pais-Vieira et al 2012 reported emotional decision making abilities in response to risk-averse performance in the rodent gambling task.

From the given literature it appears that higher cognitive functions are affected in animal model studies. Cain et al 1997; Lindner et al 1999; Millecamps et al 2004; Boyette-Davis et al 2008; and Hu et al 2010 also reported that using analgesic drugs reversed the cognitive impairments in chronic pain models. In my opinion, despite the scarce pre-clinical research, the present data provides parallel information about the pain-related cognitive impairment in clinical studies.

Mechanisms of pain-related cognitive impairment

Brain morphology and electrophysiology:

Animal model studies show alteration in anterior cingulate cortex (ACC), insular cortex (IC), somatosensory cortex –I and somatosensory area II, PFC in rats following SNL and chronic constriction injury (CCI) (Seminowicz et al 2009; Cao et al 2009). In SNI injury, an increase in basal dendrite and spine density in medial PFC contralateral to nerve injury is reported in the SNI model (Metz et al 2009), whereas increased amygdala volume and neuronal proliferation is reported in rats following the SNI (Ikeda et al 2007).

An electrophysiological study in rats correlating the rodent Gambling task demonstrated interaction between the amygdala and the PFC and pain-related cognitive impairment (Ji et al 2010); ACC, which is involved in avoidance behavior (Pedersen et al 2006); affective behavior (Johansen et al 2001); and pain related memory acquisition in the rats (Ortega- Legaspi et al 2003). In another electrophysiological study, the hippocampus is involved and affects the learning and memory functions via long term potentiation (Kodama et al 2007).

Important neurotransmitters, chemical mediators and enzymes involved in pain and cognition:

Glutamate neuro transmission and NMDA receptors are essential for long term potentiation, learning, memory (Rison et al 1995) and central sensitization (Scholz et al 2002). Pain-induced synaptic plasticity occurs in the amygdala (Fu et al 2008), ACC (Zhuo et al 2007), and hippocampus (Zhao et al 2009) in rodents following prolonged inflammatory pain. However, it is unclear if supra spinal pain induced plasticity is the extension of central sensitization in spinal cord NMDA receptors (Fu et al 2008). One speculation is that pain induced synaptic plasticity interferes at the molecular level with memory and LTP (Morarity et al 2011).

In animal models, GABA, an inhibitory neurotransmitter, is deficient, thus there is a loss of GABA inhibiting functions, which contributes to pathological pain (Enna et al 2006). Increased GABA-ergic is reported in PFC, slowing cognitive process and emotional decision making in rats (Ji et al 2010). Alteration in mono-amine neurotransmission is also reported in pain expression (Papaleo et al 2008) cognitive dysfunctions (Wood et al 2009), and attention (Scholes et al 2007). Decreased serotonin (Ford et al 2008) and dopamine levels and their metabolites in the orbitofrontal cortex are associated with impaired performance on the rodent gambling task (Pais-Vieira et al 2009b).

Acetylcholine is the mediator of cognitive processes such as learning and memory (Lucas-Meunier et al., 2003) and plays a role in descending inhibitory control of pain (Millan et al 2002). Endocannabinoid system (Graham et al 2009, Solowij et al 2008) in

PAG (Petrosino et al 2007) and nicotinic receptor in social learning and recognition paradigm (Feuerbach et al., 2008) also plays important role in pain and cognition. Reduced levels of N-acetyl aspartate are reported in PFC and ACC and impaired performance on Stroop task (Grachev et al., 2001).

In chronic pain, over expression of proinflammatory cytokines, particularly IL-1b and IL-6 (Hansson 2004, Bains et al 2007), increase astroglial stimulation in ACC (Kuzumaki et al 2007), affecting the synaptic plasticity, learning and memory. In the transgenic mice model, pain is associated with the over expression of CAMKII in the forebrain (ACC, hippocampus and amygdala) and cognition (Giese et al 1998). In PFC, pain induces the expression of Caspases (Neugebauer et al 2009), which further induces cytokines release and apoptosis in PFC (Thornberry et al 1998).

Literature shows that, in animal model studies, there is a decrease in BDNF in the hippocampus leading to cognitive impairment (Hu et al 2010), memory processing, storage, and long term memory (Duric et al 2006).

Chronic pain; Structural and Physiological Changes in Brain in the Clinical Studies:

Pain processing is complex and is facilitated by neural networks involved in perception, cognition, and emotion. Performance on cognitive tasks also depends on sensorimotor processes such as motor response, auditory and visual processing. Luerding et al 2008 attempted to link performance on cognitive test with brain morphology in FM patients. Seo et al 2012 and Smallwood et al 2013 reported abnormalities of the fronto-parietal network and different clusters or brain regions involved with pain processing respectively.

As reported, different cortical structures are involved in pain and cognitive processing (**Table# 10**). The cortical structures involved in pain processing are the inferior frontal cortex (IFC), the supplementary motor area (SMA), pre SMA, the anterior cingulate gyrus (ACC), the mid cingulate cortex (MCC) and the basal ganglia (BG) such as the caudate and the subthalamic nucleus (Apkarian et al 2005, Dosenbach et al 2006, Congdon et al 2010). These areas are involved in response inhibition, error detection, sensory, and cognitive tasks such as attention, working memory, control and the pain system (Owen et al 2005). The dorso-lateral pre-frontal cortex (DLPFC) and ventro-lateral pre-frontal cortex (VLPFC) maintain the task appropriate or inhibition, remembering, and retrieving planned acts (Owen et al 2005; Miller et al 2001). Therefore, alteration in the DLPFC and VLPFC causes a decline in working memory; executive function; inhibition; and emotional, cognitive and behavioural responses.

Other important cortical structures are the inferior temporal gyrus (ITG) and the fusiform gyrus (FG). These are part of the visual association cortex and are involved in object recognition. The inferior parietal cortex (IPC) is involved in marinating information temporally and switching attention rapidly (Ravizza et al 2004). Activity in the inferior parietal cortex is associated with pain threshold and working memory (Seo et al 2012). Increased compensatory connectivity in the frontal cortex, SMA, pre-SMA and the visual association cortex in top down modulation has been reported in chronic pain patients. Baliki et al 2008 proposed a default mode network (DMN) which consists of m-PFC (theory of mind), ACC, PCC (integration), amygdala, medial temporal lobe, medial and inferior parietal cortex and para-hippocampal gyrus. Smallwood et al 2013 (**Table #11**) divided cognitive and cortical pain processing regions into 12 clusters. These clusters show significant interconnection during the pain processing.

There are two attention systems. The ventral system or bottom up attentional circuit consists of the anterior insular cortex (IC), the ventral part of inferior frontal cortex (IFG) and the temporo-parietal cortex (Corbetta 2008, Vossel 2014). The ventral attention system is differentially engaged when pain is presented in different emotional contexts. The frontal eye field of the frontal cortex and intra-parietal sulcus of the inferior parietal lobe are components of the dorsal attention system or ‘top-down orienting of

attention' system (Corbetta et al 2008; Vossel et al 2014). Both the ventral and dorsal system show decreased activation and perfusion on BOLD. The middle frontal gyrus is the link between the two attention networks (Corbetta et al 2008). The supplementary motor area (SMA) is connected with the motor cortex and projects to the caudate nucleus (Duann et al 2009). The SMA and pre SMA are thought to be involved in the planning of motor action and response selection. Parts of parietal lobe (BA 7) project to the S1, S2 and insula (insula to amygdala) (Prevosto et al 2011), providing a direct cortico-cortical pathway for the attentional modulation of pain (Bushnell et al 2013) (**Figure 1**).

Neuroimaging studies report that chronic pain can compete with other cognitive, decision-making and affective processes (Baliki et al 2006). The evidence suggests that patients with chronic pain have gray matter as well as white matter changes within dorsolateral and medial PFC; the ACC and the insular para-hippocampal gyruses;the thalamus; STG; cerebellum and orbitofrontal cortex (OFC) regions (Apkarian et al 2004, Schmidt et al 2010, Kuchinad et al 2007). Smallwood et al 2013 reported a decrease in gray matter in the above reported region; however, Smallwood also reported an increase in hippocampal and para hippocampal gray matter. These regions are involved in cognitive and emotional modulation of pain (Bushnell et al 2013). The cortical changes or atrophy in chronic pain patients is distinct from that in patients with chronic depression or anxiety (Bell- McGuinty et al 2002, Almeida et al 2003, Yamasue et al 2003). Gray matter changes are reversible when chronic pain is treated, thus grey matter changes in chronic pain are the result of reduced dendritic or synaptic density and possible changes in non-neuronal tissue (Seminowicz et al 2007).

Brain imaging studies also show alteration in regional blood flow and chemical alteration in the sensory and nociceptive stimuli (Cook et al 2004). Seo et al 2012 studied the deactivation network including the hippocampus, para-hippocampus, middle and superior temporal poles, amygdale, m-PFC, insula, PCC, medial parietal and sensorimotor cortex. Baliki et al 2008 and Cauda et al 2010 reported decreased deactivation in DMN activity in chronic pain patients particularly in m-PFC. On correlational analysis, Seo et al 2012 found that the activation in DLPFC and VLPFC was inversely related to anxiety and depression on BDI and BAI; however, significant differences existed when the covariates were eliminated

Table# 12 shows the different cortical regions involved with chronic pain and cognition processing and the cortical changes associated with chronic pain. Napadow et al 2010 reported inter-connectivity between DMN and the insular cortex indicating that the executive attention network is hyper-integrated in the pain system. Luerding et al 2008, Burgmer et al 2009, Cook et al 2004, Kuchinad et al 2007, Robinson et al 2011, pointed out the association between memory dysfunction, pain, and structural brain changes in the medial frontal and ACC in FM. Pain and negative emotions cause activation of the fronto–PAG–brainstem circuit and the insula and superior parietal cortex (Deus et al 2006; Bushnell et al 2013). Negative emotions and analgesics cause the activation of ACC–fronto–PAG circuitry but mainly in ACC (Deus et al 2006; Bushnell

et al 2013). Miller et al 2000 reported that focusing on pain might lead to functional aberrations in the brain at molecular or synaptic levels.

Seo et al 2012 studied cortical regions using the f-MRI and noted the inferior parietal lobe was associated with the working memory network. Luerding et al 2008 reported a significant difference between verbal memory digit span-backward, short term verbal working memory (VWM) and CVLT -long term VWM. Similarly significant differences were reported for non-VWM (Corsi Block span; short term) and RAVLT. This dysfunction represents the dysfunction in frontal cortex. Amici et al 2007 reported verbal working memory deficits in DLPFC and inferior parietal cortex. Gianaros et al 2006 reported positive correlation between verbal WM and SMA, the superior frontal gyrus, and the anterior cingulate gyrus.

Chronic pain patients also have chemical and immune changes in the cortical areas of pain perception and attentional function (Kuchinad et al 2007). Chronic pain patients may have altered glutamate, decreased Acetyl aspartate in the frontal cortices (Grachev et al 2001), and a higher level of CSF- substance P (Mathew et al 2004). Alteration in dopaminergic systems that results in deficits in intracortical modulation and reward deficiency involving both GABAergic and glutamatergic mechanisms have been reported (Emad et al 2008, Kuchinad et al 2007, Wood et al 2007). PAG has antinociception properties, whereas the nucleus cuneiforms of the brainstem have reservoirs for nor-epinephrine (NE) and play a role in alertness. Dysfunction in this system has been reported in FM patients (Bingel et al 2008, Leavitt et al 2006). Beside abnormalities of antinociception system, abnormalities in the communicating structures involved in attention were also reported (Glass et al 2011).

Research Questions:

1. Whether chronic pain is associated with neuro-cognitive deficits on neuropsychological test performance?
2. What is the magnitude of the neurocognitive deficits, associated with impaired performance on neuropsychological tests?

Study rationale:

Chronic pain patients report problems with concentration; verbal fluency; processing; psychomotor speed; and immediate and long-term memory. Those deficits are often associated with depressive or psychological symptoms and medication effects (Geisser et al 1997). There is relatively little data available to help the clinician estimate the likelihood of inverse relations between pain and cognitive function (Roth et al 2005). The effects of chronic pain on cognitive functioning are vital to comprehend the scope of the problems, to formulate a differential diagnosis, and to evaluate atypical presentations in patients. There is a need to emphasize the importance of a multidisciplinary team approach to these patients' assessment and treatment.

Objectives

The goal or objectives of this study are:

a. To study the range of the specific tests and cognitive domains associated with chronic pain. For this meta-analysis and literature review, association of chronic pain with a subset of cognitive domains including: attention, learning and memory, information processing speed, psychomotor ability and executive functions were studied. Loss of function in these domains is likely to have an impact on the execution of daily tasks and, therefore, negatively affect the individual.
b. Objectively identifying the cognitive deficits in chronic pain patients provides targets for treatment and rehabilitation. Awareness of potential cognitive limitations would be important to multidisciplinary programs that require patients with chronic pain to learn new strategies to cope with their pain and cognitive dysfunction.

Hypothesis:

H: Cognitive impairments of varying types and extent associated with chronic pain on neuro-cognitive test performance can be objectively identified and are not merely subjective findings secondary to medications, depression, and fatigue and sleep impairment.

Important definitions:

Pain:

Pain is a subjective, multi dimensional experience that can have a marked impact on an individual's physiological and psychological state. The International Association for the Study of Pain (IASP) defines pain as ''an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage'' (IASP Task Force on Taxonomy, 1994). The above definition focuses on pain as a perception to be consciously experienced for which cognitive processing is required.

Pain that persists over three to six months, following the disease process or bodily injury, is referred as a chronic pain (Merskey et al 1994; Aguggia, et al 2003). The longer the pain persists, the more recalcitrant it generally becomes, the more treatment goals focus on coping with pain and its concomitants (Kulich and Baker et al 1999, Zasler et al 2011).

Cognition:

Cognition refers to the brain's acquisition, processing, storage and retrieval of information (Lawlor et al 2002). Cognition is a broad term and refers to a group of mental processes such as attention, memory, learning, reasoning, problem solving, and decision making. Cognition usually refers to information processing; mental functions and thoughts; applying knowledge; and changing preferences (Blomberg et al 2011).

Chronic pain and cognition:

Cognition describes integrative processes such as mental imaging, problem solving and perception pertinent to the experience of emotion and affect. Neurocognitive symptoms have been documented in chronic pain patients. Iverson and McCracken et al 1997 and Smith-See Miller et al 2003 reported a high frequency of symptoms such as fatigue, irritability and sleep disturbance associated with chronic pain.

The underlying mechanisms to how chronic pain affects cognitive functioning and how people perceive pain are complex and not completely understood. It is speculated that pain has a cognitive-evaluative component, requiring learning, recall of past experiences and active decision making. It is hypothesised that neural systems, neuro-anatomical pathways, and neurochemical mediators in chronic pain overlap with cognitive functioning, thus contributing to cognitive impairment. The neuroplastic changes, such neural rewiring or reorganisation in the brain, interfere with normal cognitive functioning (Hart et al 2000). The pain pathway which influences cognitive functioning is hampered by a myriad of variables and can be a consequence of the division of limited resources in discrete brain regions (Roth et al 2005).

Current evidence also supports mechanisms of central sensitization that are not present in the acute or sub acute periods (Zasler et al 2011; Finnerup et al 2010). The central pain control response encompasses the cognitive-evaluative, motivational-affective, and sensory-discriminative systems (Melzack et al 2001; Beauregard et al 2007; Browning M et al 2011). From a neurointegrative point of view, reduced ability to assign affective meaning to sensory and internal cues reflects a neural imbalance between sensory discriminative, affective, cognitive, executive and introspective functions, and emotional empathy (Apkarian et al 2001, Browning M et al 2011; Michael Noll-Hussong et al 2013).

Following are the cognitive domains that are commonly thought to be impaired by chronic pain:

Attention

Chronic pain is attention demanding and competes with attention-demanding stimuli for limited cognitive resources (Eccleston et al 1999). Chronic pain affects the attentional switching and attentional interference tasks (Munoz et al 2005; Eccleston et al 1994; Legrain et al 2009; Grisart et al 2001). Attention deficits have been demonstrated in a variety of chronic pain conditions such as fibromyalgia, diabetic neuropathy, chronic low back pain and whiplash associated disorder (WAD). Attention and mental flexibility encompass multiple functions including sustained, divided, and selective or focused attention (Sarter et al 2001).

Strong overlap exists between these attentional resources, executive functions, inhibition and mental flexibility (Sarter et al 2001). Some studies did not find any decreased attentional abilities in chronic pain patients as compared to controls (Shur et al 2003). However, other studies reported significant associations between chronic pain and sustained attention, inhibition and mental flexibility (Karp et al 2006, Verdejo- Garcia et al 2009, Sjogren et al 2000).

Executive function

Executive function is under the control of the frontal cortex and the anterior cingulate cortex of the limbic system that is involved in pain processing (Zasler et al 2011). The same brain regions also affect controls in the attention processes, working memory, and self-regulation. Chronic pain affects executive function as measured on the Wisconsin Card Sorting Test (WCST) and flexibility tasks such as Trail Making Test (TMT) (Karp et al 2006; Verdejo-Garcia et al 2009; Weiner et al 2006).

Performance on the task of attention interference or attention switching and emotional decision making require executive function (Bosma et al 2002; Eccleston et al 1994; Karp et al 2006).

Memory and learning:

Memory is a broad term and involves semantic memory, episodic memory, working memory (Park et al 2001), and prospective memory (Dick et al 2007). Working memory is the retrieval and maintenance of information (Kinnunen et al 2011). In chronic pain patients compromise in verbal working memory; working memory capacity and recall (Bosma et al 2002; Weiner et al 2006); recognition memory (Park et al 2001); and long-term spatial memory (Luerding et al 2008) are reported.

Memory deficits have been documented using the Auditory Verbal Learning Test (AVLT),Logical Memory, and Controlled Oral Word Association (COWA) in chronic pain patients (Schwartz et al 1987, Kewman et al 1991, Schmand et al 1998). Grace et al 1995 and Sletvold et al 1995 found evidence of mild memory impairment and primary deficits in attention, using the WMS-R General Memory and Delayed Recall Indices, attention, and in information processing speed on the WAIS Digit Symbol and PASAT and letter fluency (Grace et al 1995).

Information Speed processing, reaction time and psychomotor ability

Chronic pain patients have slower reaction times, psychomotor speed (Biessels et al 2007; Harman et al 2005) and perceptual learning ability (Maihofner et al 2007). Both executive function and attention are vulnerable to a reduction in psychomotor speed (Hart et al 2000; Oosterman et al 2012).

CHAPTER 2: METHODS

Literature search:

A systematic review was conducted according to the Cochrane systemic review and meta-analysis guidelines. The prior review protocol was discussed with my supervisor, members of supervisory committee and my advisor. The literature search strategy was developed in collaboration with St. Joseph's Hospital Library and McMaster University Library. Studies published between 1946 to August 2013 were retrieved using the Ovid Medline. The key words used were broad but specific to cognitive functions (see the supplementary sheet for key words and literature reviews). The key words to search literature were divided into three main categories such as chronic pain, cognitive domains and neuro-psychological measurement. Each category was further explored using the mesh words (see the attached supplementary sheet for literature review strategy). All selections in each category were combined with "OR" in order to provide the total number of studies in that particular category. In the end, all three categories were combined using "AND", which gave the total number of studies that were reviewed. Based on the above criteria, 262,222 studies in chronic pain category, 423,626 studies in neuro-cognitive domains and 77,822 studies in neuropsychological testing were obtained. Combining the three categories reduced the number to 1393 studies. Literature search strategy was further restricted to humans and the English language which gave total 1182 studies for review. The above data was reproducible, the search was tried several times and the same result occurred each time (**see attached literature search strategy in appendix**).

Study selection (inclusion and exclusion criteria):

As mentioned previously, the study selection was limited to humans and the English language. The literature screening and selection was made according to the PRISMA Flow diagram and *"Chapter 2 of Clinical Epidemiology; How to Do Clinical Practice Research by Brian Haynes; Third Edition"*. The majority of studies included patients with chronic pain syndromes involving mixed or multiple sites, or whiplash injuries, chronic back pain, or fibromyalgia. The neuro-psychological tools used in each study were cognitive domain specific (*A Compendium of Neuropsychological Tests, 3rd edition*). An overview of the studies according to cognitive domain is given in attached supplementary sheet.

Inclusion criteria:

Studies were included after abstract review. If the methodology of the study was not clear than the whole article was read. Articles were reviewed twice to avoid missing any important articles.

- The studies to be included in this review had to evaluate cognitive functions in association with the chronic pain.
- The studies were experimental design that compared the cognitive functions in chronic pain patients with normal controls.

Exclusion criteria:

The following were our exclusion criteria for the literature review:

- Studies that studied the effects of treatments such as analgesics, morphine or opioids, psychological treatment or relaxation techniques
- Previous stroke, traumatic brain injury, neurodegenerative or neuroinflammatory conditions such as SLE, dementia, Parkinson's disease etc.
- Any other systemic conditions such as underlying cardiac conditions or any other systemic conditions that associated with depression or psychological conditions
- Adult patients who were afflicted with juvenile rheumatoid arthritis or any studies of children
- Pain studies of malingering patients
- Chronic pain studies with substance and or alcohol abuse
- Chronic pain studies that focused on motor or muscular components or somatosensory components; the patient's acceptance of adjustment to the chronic pain; or couple, spouse or family response to chronic pain
- Studies that did not study cognitive function but only focused on psychological variables
- Correlational studies and studies where the mean values and SD were not given
- Studies of psychological conditions and depression
- Studies that compared different pain groups such as chronic back pain with fibromyalgia but did not have control participants
- Studies that compared chronic pain patients with traumatic brain injury only, but did not have control participants
- All review articles, meta-analysis, editorials or letters to the editors were excluded
- The studies using electrophysiological measures or imaging techniques were excluded

Total of 1182 studies were selected for screening. Out of those, 229 articles were selected for eligibility. The search was further narrowed down to 56 studies in qualitative studies and 23 studies were included in quantitative synthesis meta-analysis (**See PRISMA flow diagram; Appendix for the reasons**)

Risk of bias assessment:

Risk of bias assessment was performed using the NewCastle- Ottawa risk of bias tool (**See attached tool and guidelines in appendix).** There are three components of the assessment: selection, comparability and exposure. Selection is divided into four subcomponents: case definition, case representation, control selection and control

definition. Each subcomponent is supposed to get one star. Comparability has two sub components: control for confounding factors and additional factors. Studies can get maximum of two stars in this component. The third component is exposure that is further sub divided into ascertainment of exposure, methods of ascertainment for case and control and no response rate. Studies can get maximum of three stars in this domain. Scoring details can found in the NewCastle Guidelines or manual (attached in appendix and tables section).

Inter-rater reliability was done between me and my student advisor. If a discrepancy was found, we both discussed the rationale and the study method of the article **(See Risk Bias Assessment in the appendix**).

Data extraction:

The data was initially extracted on Excel spread sheets (**See Excel data sheet in the attached appendix**). Before starting data extraction, studies were reviewed as to whether the studies used any depression or anxiety measuring tools. The data recorded cognitive measuring tools, pain measurement tools if stated in the articles, mean and standard deviation for each group, p-values, sample size (patient and control) and the study reference. The results were reviewed three times to ensure the accuracy. Results from all the selected studies were included whether the study showed negative association or not. Data was then reviewed by my advisor and if any discrepancy in the data was found, the articles were re-examined and the results were corrected if necessary. We calculated pooled a standard deviation and effect size from the means and standard deviations given in the studies.

After compiling, the data was sorted according to the cognitive tests. Cognitive tests that were reported in three or more studies were included this meta-analysis. Cognitive tests that were reported in less than three studies were not included in this meta-analysis. This provided further sub groups or subanalysis of data according to the cognitive domains and helped reduce the heterogeneity.

Data analysis:

After compiling the pooled SD, the effect size and weight percentage were calculated. Data for each cognitive test were pooled when results were available from at least three studies. If the study compared different pain types separately to controls, in that case,each pain type in a study was considered separate experiment. Studies were excluded from the meta-analysis if the mean and standard deviation values could not be estimated from group-level statistical results.

The statistically significant heterogeneity was determined on the basis of $I^2 > 60\%$ (Higgins et al 2008). The principal advantage of I^2 is that it can be calculated and compared across meta-analyses of different sizes, across different types of study, and

using different types of outcome data. Effect estimates were interpreted as small (0.2), moderate (0.50), or large (0.80) according to Cohen et al 1998.

CHAPTER 3: RESULTS

From the 1946 records identified by the search methods, the full text of 229 studies was retrieved (**see PRISMA flow chart; appendix**). Of these 229 studies, 23 met the inclusion criteria. As reported in the methods section, only tests that were reported in three or more studies were included. Based on this protocol, three studies were excluded: Antephol et al 2003, Park et al 2001, and Veldehujezin et al 2012. Data was collected in terms of mean and standard deviation data and to clarify the cognitive deficit construct being testing. The key characteristics of the included studies are summarised in the Excel spreadsheet (**See appendix**).

Risk bias assessment:

NewCastle Ottawa (NC-O) guidelines were employed for the risk of bias assessment **(See Appendix for the Risk Bias Assessment)**. For data collection and reviewing studies, particular attention was given to study samples as to if blinding was done, how samples were recruited and associated medical and psychological conditions. DiStefano et al 1995 did not mention the proper definition of his cases (whiplash patients). Ho Kim et al 2012 and Verdejo Garcia et al 2012 did not have the true representation of their cases. Bosma et al 2002 and Leavitt et al 2006 did not have the true representation of the control and their controls did not meet the control criteria or defined in NewCastle Ottawa (NC-O) risk bias assessment manual. Gimse et al 1997, Leavitt et al 2006, Schmand et al 1998 and Sjogren et al 2005 did not meet the control definition criteria for NC-O risk bias assessment.

Bosma et al 2002, Grisart et al 2001, Landro et al 1997, Schmand et al 1998, Suhr et al 2003, Walitt et al 2008 and Weiner et al 2006, only reported “no significant group difference were found” between the control and chronic pain group IQ. According to the NC-O risk bias assessment, these statements should not be scored. 40% of the total studies did not compare case-control according to the NC-O bias risk assessment protocol. 50% of studies only compared for one demographic domain such as age or IQ. Only two studies, Oosterman 2011 and 2012, compared case-control according to the age and IQ and other demographic profiles.

In this analysis, none of the studies were blinded. Probably blinding in these studies is not possible as chronic pain patients due to the physical discomfort that would be obviously apparent, which would mask the blinding outcome. Method of ascertainment and participant’s response were reported in all the studies and the same neurocognitive tests were applied to both chronic pain and to control population.

An important point that was not the part of the New Castle- Ottawa risk bias assessment protocol, but was noticed while reviewing the literature, was that, except for Ho Kim et al 2012, no other author had selective outcome reporting bias. Ho Kim et al 2012 did not report WCST.

Pain population:

Table # 13 shows different types of chronic pain patients that were studied/ included in this meta-analysis. Overall, there were 1193 patient participants in the selected studies. Fibromyalgia (FM; 49.70%) was the dominant pain type, followed by musculoskeletal (24%), non specified (15.25%) and whiplash pain (14%). However, Grisart et al 2001, Oosterman et al 2011, and Oosterman et al 2012 did not report separate results for visceral, musculo-skeletal pain, and neuropathic pain; therefore the chronic pain patients from these studies were categorized as non specified pain.

How cognitive functions were evaluated:

All studies included in this meta-analysis used valid and reliable neuro-psychological tests. All tests required a patient response to assess the cognitive function; however, reporting varied among the neuropsychological tests. If a neuropsychological test had subtests such as WAIS- Letter sequence number, WAIS-arithmetic or RAVLT immediate and delayed recall, all those subtests were considered as separate analysis and were reported separately **(Table# 14).**

Table # 15 shows how the responses were scored in different studies. Scoring depended mainly on the cognitive test. Most of responses required a number or sum of correct answers or time to complete. Most of the authors followed standard reporting criteria with few exceptions. Di Stefano et al 1995 reported the mean error score on the PASAT, whereas others reported the number of correct responses. Bosma et al 2002 reported as percentile score for PASAT. Schmand et al 1998 and Oosterman et al 2012 log transformed their scores.

A total 24 test outcomes or constructs (**See attached appendix**) were derived from different neuropsychological tests. Only WCST required a number of categories or percentage of Perservative errors. In this meta-analysis and as mentioned in the methodology section, if a cognitive domain was reported but author did not report the test name, the cognitive domain was not included in the analysis e.g. Antephol et al 2003, Park et al 2001 and Veldhuijzen et al 2012. Antephol et al 2003 measured the accuracy rate verbal memory and spatial memory. Park et al 2001 did not report which test was employed to measure the psychomotor speed and verbal fluency. Veldhuijzen et al 2012 used Multi Source Interference Task (MSIT). Veldhuijzen et al 2012 also measured Stroop Color Word Test differently as compared to other authors.

Reporting outcomes:

Corsi Block- Spatial Forward Test:

Visuospatial working memory (VSWM) is the working memory component that maintains spatial and visual information to ensure the formation and manipulation of

mental images. The VSWM was assessed with the Corsi Block- spatial forward test. Canovas et al 2009, DiStefano et al 1995, and Ho Kim et al 2012 used this test to assess the VSWM. There were a total of four comparisons from three studies and 80 patient participants from all the studies. The dominant pain type was whiplash. The heterogeneity was 0%; however no significant effect= -0.26, P= 0.10 as observed.

ROCF- immediate and delayed recall:

ROCF is the measure of visuospatial constructional ability and visual memory (Yamashita et al 2009).

Three comparisons were done in ROCF- immediate recall (Bosma et al 2002, Ho Kim et al 2012, and Lee et al 2010). Borderline non-significant effect (P= 0.08) was noted and the heterogeneity was 90%.

Focusing on ROCF- delayed recall, five comparisons were done in four studies (Bosma et al 2002, Ho Kim et al 2012, Lee et al 2010 and Suhr et al 2003(Fibromyalgia and chronic pain)). Significant effect (0.02) was noted showing chronic pain patients performed worse than controls. However in this construct the heterogeneity was 67%.

In both comparisons, fibromyalgia was the dominant pain type.

Digit span test:

Digit span test is the measure of working memory and attention. Three subtests of the Digit span test were studied to evaluate verbal working memory: the number of digits recalled in forward direction, the number of digits recalled backwards, and the number of digits recalled in forward and backward directions. Fibromyalgia was the dominant pain type in digit span forward and digit span- backward test. Whiplash pain was the dominant pain type in Digit span (backward and forward).

Three studies, Ca Novas et al 2009, Ho Kim et al 2012, and Landro et al 1997, studied working memory using Digit span-forward. The overall effect was not significant (0.19; P= 0.36).

Canovas et al 2009, Ho Kim et al 2012, Landro et al 1997 and Oosterman et al 2011 used digit span-backward. Moderate effect (0.39, P= 0.009; CI= -0.68, -0.10, I^2=0%) was noted, showing chronic pain patients performed worse than healthy controls.

No significant effect (-0.20, P= 0.12) was noted on WAIS digit span- forward and back (DiStefano et al 1995; Leavitt et al 2006, Suhr et al 2003).

Wisconsin card Sorting Test (WCST):

Suhr et al 2003 and Verdejo Garcia et al 2009 studied executive function, distractibility and working memory using the Wisconsin Card Sorting test. Both authors measured WCST preservative errors and number of categories. The patient group showed

a borderline effect (0.29; P= 0.07; heterogeneity 63%) on WCST- number of categories. However no effect (0.15; P= 0.33) was noted on WCST- preservative errors.

Digit symbol test:

Digit symbol is the measure of psychomotor speed, visual scanning, incidental learning memory and free recall (Joy S et al 2004). Four comparisons were done from the four studies (Grace et al 1999, Suhr et al 2003, Lee et al 2003 and Schmand et al 1995). Total patient participation in this comparison was 406 and the dominant pain type was fibromyalgia (76.86%). Moderate effect (-0.34, 0.00001; I^2= 8%; CI= -0.46, -0.22) was noted, showing that chronic pain patients performed worse than healthy control.

Trail making test (TMT) A & B:

Trail making test (TMT) - A is the measure of psychomotor speed and visual scanning. Seven studies used TMT-A and 10 comparisons were made. There were 288 patient participants in TMT-A comparisons and Whiplash (55.9%) was the dominant pain type. Moderate effect (0.30, P= 0.0002; CI; 0.15, 0.49; I^2= 0%) was noted.

TMT-B is the measure of mental flexibility and complex psychomotor speed. Eight studies used TMT-B using 11 comparisons with a total 451 patient participants and fibromyalgia (53.21%) was the dominant pain type in this construct. Moderate effect (0.38, P= 0.00001; CI= 0.25, 0.52, I^2= 32%) was noted, showing chronic pain patients performed worse than healthy controls.

Test of Every Day Attention (TEA):

Test of Every Day Attention (TEA) is used to assess the four different domains of attention such as selective attention, sustained attention, switching attention, and auditory-verbal working memory (Robertson et al 1994; Dick et al 2002 & 2008).

Dick et al 2002 and Dick et al 2008 studied TEA-working memory in four comparisons. There were a total of 90 patient participants in working memory, sustained memory and selective attention and 60 patient participants in switching memory domains. Fibromyalgia was the dominant pain type in all these comparisons. Large effect (-0.92; P= 0.00001, CI= -1.24, -0.61; I^2= 33%) was noted on the working memory construct. Moderate effect (-0.44, P= 0.02, CI= -0.80, -0.07; I^2= 0%) was noted on the measure of TEA switching attention. Large effect (-0.77, P= 0.00001, CI= -1.07, -0.46, I^2= 1%) was noted on the measure of sustained attention. Large effect (-0.87, P= 0.00001, CI= -1.18, -0.56, I^2= 0%) was noted the measure of selective attention.

Stroop test:

Stroop test is the measure of inhibition, executive function, cognitive flexibility and selective attention. Stroop test has three components: Stroop- Color, Stroop Word and Stroop Color-Word. Four comparisons were done in three studies. Total patient participants in each comparison were 147. Whiplash was the dominant pain (44.21%) type in each comparison. Moderate effect (0.37, P= 0.003, CI= 0.13, 0.61; I^2= 0%) was

noted on Stroop C test. Moderate effect (0.31, P= 0.01, CI= 0.07, 0.55, I^2= 58% on Stroop Word and moderate effect (0.35, P= 0.004; CI= 0.11, 0.59; I^2= 0%) was noted for Stroop C/W, showing that chronic pain patients performed worse than healthy control.

Rye Adult Learning Test (RAVLT):

Rye Adult Learning Test (RAVLT) is a measure of learning, verbal recall and verbal memory. Three components, immediate recall, delayed recall and delayed recognition, were measured. In all three comparisons, whiplash was the dominant pain type, 47.31%, 44.5% and 54.8%, respectively.

Grace et al 1999, Suhr et al 2003, Ho Kim et al 2012, Gimse et al 1997and Schmand et al 1998 studied RAVLT- immediate recall. Moderate effect was noted for RAVLT- immediate recall (-0.52, P= 0.00001, CI= -0.74, -0.31, I^2= 47%).

Schmand et al 1998, Gimse et al 1997, Ho Kim et al 2012 and Suhr et al 2003 measured RAVLT- delayed recall. Moderate effect was noted for RAVLT- delayed recall (-0.57, P= 0.00001, CI= -0.83, -0.31, I^2= 0%)]

Schmand et al 1998 and Suhr et al 2003 studied delayed recognition. Moderate effect (-0.51, 0.0005, CI= -0.80, -0.23; I^2= 0%) was noted.

Paced Auditory Serial Addition Test (PASAT):

PASAT is the measure of sustained attention, divided attention and working memory. Grace et al 1999, Di Stefano et al 1995, Bosma et al 2002, Suhr et al 2003, Sjogren et al 2005, Leavitt et al 2006 and Gimse et al 1997 studied these cognitive domains. Whiplash was the dominant pain type (32.325%) and total patient participants were 297. Moderate effect (-0.43, P= 0.00001, CI= -0.60, -0.26, I^2= 42%) was noted, showing chronic pain patients performed worse than healthy controls.

Tables# 16 and #17 give a summary of the cognitive tests, the cognitive domains measured and their effect size. In summary, no significant effect was found on the measure of Corsi Block- spatial forward, ROCF- immediate and delayed recall, WCST- Perservative errors, WAIS- digit span forward, and digit span (forward and backward). Border line non-significant effect was found was found in WCST- number of categories. Significant effect was found in the remaining cognitive tests such as PASAT, RAVLT- immediate and delayed recall and delayed recognition, Stroop test, TMT- A& B, TEA, and digit span-backward test.

Table# 17 gives a summary of the cognitive domains that were measured in this meta-analysis. No significant effect is noted on the measure of visuo-spatial or non-verbal memory. Two out of three comparisons (Corsi Block- forward spatial, ROCF- immediate and delayed recall) failed to show significant effect in chronic pain patients. ROCF- delayed recall showed significant effect. However, the heterogeneity was high. Significant effect is noted on the measure of psychomotor speed, mental flexibility,

switching attention, sustained attention, selective attention and divided attention. Chronic pain patients had difficulty on immediate and delayed memory recall, recognition of the learning, and memory tests.

The results of this meta-analysis show poor working memory performance in chronic patients as compared to the healthy controls; no significant effect was noted on forward digit span component. Similarly, on executive function measurements, no significant effect was seen on WCST test; however, significant effect was seen on all the components of Stroop test.

CHAPTER 4: DISCUSSION

Previously it was believed that neuro-cognitive impairment associated with chronic pain was subjective and secondary to associated factors such as medications; depression or anxiety; sleep disruption; or medication use. Earlier studies have not found a consistent association between subjective complaints and objective performance on neuropsychological tests (Landro et al 2013). Variability in cognitive findings could be due to different assessment protocols or experimental approaches measuring the certain cognitive mechanism (Leavitt et al 2006). Different neuropsychological tests have degrees of utility in detecting the presence of cognitive impairment, because some aspects of memory are working adequately and other aspects are significantly impaired (Cicerone et al 2002). This is evident in studies done by Lee et al 2010 and Park et al 2001. Lee et al 2010 found a decline in processing speed; Park et al 2001 did not find a decline in information processing speed, but found deficits on working memory, verbal skills and recognition memory. Apkarian et al 2003, Suhr et al 2003, Veldhuijzen et al 2006, Karp et al 2006, and Verdejo-Garcia et al 2009 failed to show differences on the measure of inhibition, mental flexibility, letter fluency and sustained attention.

The main focus of this meta-analysis was to determine the evidence that chronic pain is associated with impaired performance on the neuropsychological tests. The main finding is that performance on most of the neuropsychological tests was significantly associated with objective cognitive impairments. The results of this meta-analysis corroborate and extend a previous narrative review, Hart et al 2000 and Morarity et al 2011, suggesting a cognitive dysfunction association with chronic pain.

Probably this is the first meta-analysis that measures or focuses the overall or broader extent of the cognitive impairment associated with chronic pain. This meta-analysis shows that chronic pain patients, compared to healthy controls, have significant objective problems on tests of working memory, attention, immediate and delayed recall, visuomotor tracking, and cognitive flexibility. In this meta-analysis, higher heterogeneity for pooling due to different experimental approaches was expected. Therefore, studies were combined according to the cognitive test to reduce the heterogeneity. Results from different test constructs show variable effects such as small to large effect on different cognitive domains.

In this analysis ROCF-immediate recall, delayed recall and Corsi- Block spatial forward are separate tests to measure visuospatial memory. Corsi- Block and ROCF-immediate recall failed to show significant effect. ROCF-delayed recall showed significant effect; however the heterogeneity was high (67%). Although on ROCF-delayed recall the effect is significant, but increased heterogeneity may not show if true effect exists. Out of the five individual studies in these constructs, only Ho Kim et al 2012 showed significant effects. In individual studies, Lee et al 2010, Bosma et al 2002 and Suhr et al 2003, the effects on ROCF were not significant.

Heterogeneity is low in Corsi Block Spatial Forward (0%) but higher in ROCF-immediate recall (90%). Neither of the individual studies in Corsi Block Spatial Forward showed significant association between chronic pain and impaired performance on Corsi Block Spatial Forward. In ROCF- immediate recall and delayed recall, all the individual studies showed significant negative association between chronic pain and performance on ROCF- immediate and delayed recall except for Suhr et al 2003 in ROCF- delayed recall. ROCF is a complex test that requires attention, visuospatial perception, motor function and organizational abilities. Visual memory test depends on recognition paradigm. Recognition paradigms are less attention demanding and less sensitive to disruptive effect of the chronic pain (Oosterman et al 2011).

Verbal learning and memory was measured with the Rye Adult Learning Memory (RAVLT). This test has three components such as RAVLT- immediate recall, delayed recall and delayed recognition. Moderate effect was noted for all the three components of RAVLT. Verbal memory refers to memory of words and abstractions involving language. Grace et al 1999, Bosma et al 2002, Park et al 2001 and Weiner et al 2006 reported poor verbal memory performance in chronic pain patients. Weiner et al 2006 also reported decreased performance on the MMSE in chronic pain patients. Memory components such as category fluency and semantic memory were not measured in this meta-analysis. Episodic memory is related with the events embedded in a temporal and spatial context, whereas large amount of knowledge about categories and objects is stored in semantic memory (Landro et al 1997). Language disruption does not represent the predictor of the attentional disruption as the semantic process is more automatic process and is less interrupted by the chronic pain (Grisart et al 2001 and Grisart et al 2002). However, category fluency performance measures the semantic memory functioning that requires strategy search and retrieval process. Performance on category fluency tests depends on executive function (Weiner et al 2006) and may be compromised in chronic pain patients.

Results on executive function are mixed. In this meta-analysis, Stroop test and Wisconsin Card Sorting Test measured the executive function. Stroop test is the measure of executive function, interference, selective attention and inhibition (Bosma et al 2002, Walitt et al 2008 and Schmand et al 1998). Stroop test has three components:Stroop color, Stroop Word and Stroop Color-Word. Performance on the Stroop test depends on psychomotor speed, attention and interference, which are compromised in chronic pain patients (Hart et al 2000, Mead et al 2002, Oosterman et al 2012). The Stroop Colour-Word test requires the inhibition of one type of stimulus while responding to another stimulus (Mead et al 2002). Therefore performance on the Stroop test is dependent on inhibition and selective attention and both of these domains are compromised in chronic pain patients.

Executive functions are measured by the WCST, interference (Stroop Color-Word) and mental flexibility such as Trail making tasks. Only two subtests of WCST such as number of preservative errors and number of categories met the inclusion criteria of this meta-analysis. However the effect was not significant in either of these two

subtests of WCST. This observation on WCST is in line with Suhr et al 2003, who did not reported association between poor performance on WCST and pain. The WCST is a multi-component task and the performance on WCST mainly depends on the rule detection and to some extent on the flexibility and working memory skills. Lower number of categories on WCST performance indicates compromised rule detection, whereas increased non-Perseverative errors are related to increased distractibility (Kaplan et al 2006; Verdejo Garcia et al 2009).

Multiple functions are commonly attributed to the concept of executive function and attentional control. It is one of the most poorly understood domains (Oosterman et al 2012). The mechanism of attention and executive function decline in chronic pain patients is unclear. It is hypothesized that chronic pain, attention and executive function share common resources (Eccleston et al 1999). Decline in executive function and attentional sources could be the result of the attentional demand of chronic pain (Morarity et al 2011; Sjogren et al 2005).Bosma et al 2002,Verdejo-Garcia et al 2009 and Weiner et al 2006 reported that execution of more complex switching attentional tasks that require interference and inhibition are more affected as compared to less complex or automatic tasks.

In this analysis, moderate effect was noted on PASAT. This result is in line with Grace et al 1999, DiStefano et al 1995, Gimse et al 1999 and Leavitt et al 2006. PASAT measures the divided attention and the performance on PASAT depends on processing speed. Performance on PASAT challenges the concentration skills both in terms of degree of difficulty as well as duration (Grace et al 1999). Performance on the PASAT depends on adding ability, sustained attention, processing speed, and executive skills (Leavitt et al 2006).

Information processing speed is how quickly a person can make simple perceptual decisions; whereas working memory is the measure of how much information a person can store and process (Park et al 2001). Working memory and information processing speed are the building blocks of cognitive function and long term memory (Park et al 2001). Sletvold et al 1995, reported a decline in information processing speed and working memory in chronic pain patients. Information processing speed mediates the relationship between physical function and pain (Veldhuijzen et al 2012).

Dick et al 2002 and 2008 measured different domains of attention such as working memory, sustained attention, selective attention and switching attentions using Test of Every Day Attention (TEA). Significant large effect was noted for working memory, sustained attention and selective attention and moderate effect for switching attention. Dick et al 2002 measured the TEA performance between chronic musculo-skeletal pain, rheumatoid arthritis (RA) and FM and pain free control. There were significant group differences on the measure of selective attention, sustained attention and working memory between pain groups and control but no significant performance difference between FM and RA patients. The performance on the repeated measure of

selective and sustained attention represents slowing of mental flexibility and fatigability in chronic pain patients (Oosterman et al 2012).

Impairments related to attention are one of the most known cognitive effects of chronic pain (Hart et al 2000). The attentional control system not only controls worrying and rumination but also redirects attention away from pain (Eccleston et al 1999). Eccleston and Crombez et al 1999 argued that chronic pain was a chronic interruption and in fact other tasks have to compete with pain in order to gain attentional resources. Higher expectation of pain from a task or previous reward alters the attention, while attention to a task may promote ongoing action and maintain desired behaviour (Gazzaley et al 2012). Deficient attentional control might contribute to maintenance of the chronic pain and should be systematically explored in future studies.

Conflicting arguments have been made by different authors about the decline in working memory and attentional resources associated with chronic pain. Landro et al 2013 reported that subjective complaints in chronic pain patients are related to basic aspect of executive functions, attentional or inhibitory control but not to working memory. Oosterman et al 2011 reported that after controlling for attention, the difference on working memory was not significant. Dick et al 2007 examined attention and working memory performances in chronic pain patients and reported that patients with impaired attention also had impaired working memory. However, Antephol et al 2003, Dick et al 2008, and Berryman et al 2013 reported that impairment in working memory will limit planning, mental flexibility, decision making and disrupts attention. It is also hypothesized that working memory competes with processing and prioritizing the allocation of attention according to implicit and explicit cognitive goals (Legrain et al 2009).

Digit span is the measure of index of the working memory and intelligence. This analysis showed a decline in WAIS- backward domains but not in digit span- forward and digit span, which were not significant. Variable effect size is noted on all the digits span constructs, ranging from small to moderate. It is hypothesized that cognitive impairment depends on the complexity of the task as is evident in WAIS –forward and backward construct of this meta-analysis. This observation is in line with Grisart et al 2007 and Landro et al 1997, that effortful –automatic processing requires more attentional demand thus interferes with other cognitive resources that require effortful capacity. Digit span test-backward requires more effort, therefore poor performance is noted on WAIS-backward but not on the forward.

Digit symbol, TMT-A and TMT-B are measures of information processing speed, visual scanning and mental flexibility. TMT-A is a measure of visual scanning and psychomotor speed. Small to moderate effect was noted on the measure of TMT-A. Sjogren et al 2005, Lee et al 2010, Ho Kim et al 2012 reported impairment on the measure of psychomotor speed.

Performance on the TMT-B requires divided attention for successful performance but is commonly regarded as a test of mental flexibility (Kortte KB et al 2002). In this analysis, moderate effect size was noted on the measure of TMT-B. An important observation reported is by DiStefano et al 1995 who examined performance on TMT-B at base line in whiplash patients and then at 6 and 24 months follow ups. Impaired performance was noted at the base line level in acute pain conditions. No impaired performance was noted at follow up examination in asymptomatic patients but impaired performance was noted in chronic pain patients.

In this analysis reaction time was not measured. However slower reaction time has been reported in Park et al 2001, Iverson et al 2007 and Veldhuijzen et al 2012 studies. Decreased reaction time on the SCWT and MSIT reflects the problem in the underlying mental processing speed, psychomotor slowing or both (Veldhuijzen et al 2012).An explanation for slower reaction time is that patients with FM may exaggerate or put out less effort while performing on those tests (Gervais et al 2001, Kool et al 2009). Iverson et al 2007 reported slow reaction time performance in fibromyalgia patients,but not the number of errors measured on the test, it is unlikely that these findings merely represent symptom exaggeration.

Landro et al 2013 reported that patients with generalized and neuropathic pain performed poorer as compared to patients with localized pain. However, in this meta-analysis, the widespread pain groups were fibromyalgia and to some extent whiplash disorders. This analysis does not focus on severity and duration of the chronic pain on one's cognitive impairment, which could be a significant contributing factor. However, cognitive dysfunction according to pain type is not the goal of this analysis.

Chronic Pain and Associated Confounding Factors

It is commonly believed that cognitive impairment in chronic pain patients is secondary to associated confounding factors such as depression, anxiety, fatigability or medication use. Other important confounding factors are litigation, malingering and coping style. No specific analysis or literature search strategy was developed to measure the effect of these factors on cognitive impairment in chronic pain patients.

Chronic pain and psychological factors:

Psychological symptoms such as anxiety, depression and irritability are often reported as the confounding factors. Screening for psychiatric conditions is important as PTSD, depression and anxiety are often associated with working memory deficits (Galletly et al 2008) and have known co-morbidity with chronic pain (Otis et al 2003). However, the exact relation between psychologic factors and the recovery process has yet to been determined (Radanov et al 1994, Cote et al 1997).

Conflicting statements have been reported about the correlation between chronic pain and psychological factors. Grace et al 1999 showed modest correlation between trait anxiety, pain severity and performance. Suhr et al 2003 reported that depression and fatigue was significantly related to memory performance and psychomotor speed respectively. Martelli, M.F et al 1999 reported chronic pain patients demonstrate phobic responses to anticipated initiation of or increase of pain. Ho Kim et al 2012 did not reported significant performance difference when depression was controlled on RAVLT but did report a difference on KCFT (Korean version of ROCFT).

Although few studies reported the relationship between psychological and cognitive impairment, the cognitive deficits persist when these variable are accounted for (Grisart et al 1999, Dick et al 2008). Grisart et al 1999 measured anxiety trait score x pain and found that anxiety traits were not significantly correlated with cognitive impairment. On the other hand, Bosma et al 2002 and Dick et al 2002 reported that cognitive experiences in whiplash and FM patients do not resemble the pattern found in patients with psychological disorders. Chronic pain patients suffer cognitive impairments over and above the effects of depression and anxiety (Park et al 2001). Landro et al 1997 found that patients with fibromyalgia and depression were impaired on the Randt Memory Test, Code Memory Test and word fluency. These tests required effortful processing for these tasks. Sletvold et al 1995 and Landro et al 1997reported decline in psychomotor speed in FM patients with and without depression on PASAT, Digit Symbol Test and reaction time tests. Landro et al 2013 demonstrates that levels of anxiety did not affect the association between subjective complaints and objective performance.

Recent data demonstrating the presence of brain atrophy in patients with CLBP suggest a pattern of atrophy distinct from that in patients with chronic depression or anxiety (Bell- McGuinty et al 2002, Almeida et al 2003, Yamasue et al 2003). Thus,

chronic pain patients with memory problems display measurable and substantial evidence based on psychometric impairment.

Chronic pain and medications:

Medications are thought to be an important confounding factor. Sjogren et al 2000 reported that medications are negatively associated with cognitive performance; however, in their 2005 study, Sjogren did not find association between morphine dose and performance on neuropsychological testing (Sjogren et al 2005).

Gimse et al 1997, Radanov et al 1993 and Verdejo Garcia et al 2009 did not report significant difference on neuropsychological perform0ance in chronic pain patients taking oral opioids. Dick et al 2008, Canovas et al 2009, Kessel et al 2000, Jamison et al 2003 and Tassin et al 2003 reported the protective effect of pain medications, including opioids and antidepressants, on cognitive processes such as cognitive flexibility, short and long term recall. In Dick et al 2008, study patients taking a stable opioid dose performed better than patients not taking medications.

The use of opioids use either improves the cognitive performance or does not affect the cognitive performance on electrophysiologic testing (O'Neil et al 2000, Lorenz et al 1997). There is substantial inter individual and inter-opioid variability in this phenomenon (Allen et al 2003). Therefore,adverse neuropsychological response should not erect a barrier to proceeding with pain medication use including opioids, in which case pain reduction ultimately can result in improved cognitive function.

Motivation, coping style and somatic awareness:

Coping styles (Soderlund et al 1999) and lack of motivation (Bosma et al 2002; Keller et al 2000) might have a negative association on recovery and neuropsychological performance. Chronic pain patients with increased pain and somatic awareness had performance difficulty on attention demanding and switching tasks (Eccleston et al 1999 and Grisart et al 1999). However, Canovas et al 2009 did not report association between spatial memory tests and motivational factors.

The exact relationship between coping style, functional outcome and the relationship between pain and physical performance should be further explored in future research.

Chronic pain and head injury patients:

Hoge et al 2008 reported chronic pain is physiologically linked to brain injury. Grigsby et al 1995 compared neuropsychological performance of chronic pain patients with head injury patients and noticed that chronic pain patients performed worse than head injury patients on the measure of information processing and short term memory.

Smith-SeeMiller et al 2003 did not report a difference between chronic pain patients and mild traumatic brain injury patients on the Rivermead Post Concussion Questionnaire (RPCQ) for noise sensitivity, sleep disruption, depression, memory problem, concentration problem, processing time to think, double vision, or restlessness (Smith-SeeMiller et al 2003).

Gender:

In this meta-analysis and literature review, not a single study compared the performance between genders. The chronic pain groups in Park et al 2001 and Verdejo Garcia et al 2009 included only females; whereas, the chronic pain group in Lee et al 2010 included only male patients. Thus, it remains unknown whether gender of the chronic pain patient impacts differentially on neuropsychological test performance.

Litigation and malingering:

FM patients who are on disability benefits or seeking disability benefits show less effort on neuropsychological tests (Gervais et al 2001) and may consciously malinger their symptoms (Suhr et al 2003). Schmand et al 1998 compared both malingering and non-malingering WAD patients and reported that both groups performed below the normal controls but similar to traumatic brain injury patients on memory and concentration. Distefano assessed malingering using Block Design and Similarities subtests from the WAIS-R, which serves as another purpose and assesses malingering, however did not find correlation between the whiplash and malingering. Although it is never possible to safeguard completely against malingering, it is unlikely that whiplash patients will malinger in a well organized way and consistently simulate their performance on the same tests (Distefano et al 1995). Symptom exaggeration has been reported in fibromyalgia patients but objective cognitive impairment on neuro-psychological testing shows that chronic pain patients certainly have a decline in cognitive performance that cannot be explained completely by malingering or litigation (Distefano et al 1995, Schmand et al 1998).

Strengths and weaknesses of this meta-analysis:

An advantage of a meta-analytical approach is that it does not suffer from several shortcomings of traditional qualitative narrative reviews. Several comprehensive narrative reviews of cognitive impairment association with chronic pain exist; however, this meta-analysis is the first review that analyzes the broader aspects and extent of the different cognitive impairments associated with chronic pain. Another strength of this meta-analysis is that the cognitive domains are studied according to the neuropsychological test performances, which reduces the risk of increased heterogeneity of variance.

A **limitation** of the present study is the inconsistent number of participants in studies and ultimately inconsistent number of participants in each construct. The most important limitation is the risk of bias in the selection and reporting of the results. Leavitt et al 2006, and Sjogren et al 2005 (MMSE score 23-24) reported chronic pain patients who appeared to demonstrate cognitive deficits which increase the validity threat. Seven studies (DiStefano et al 1995, Gimse et al 1997, Ho Kim (only physical examination), Oosterman et al 2011 and et al 2012, Sjogren et al 2005, Weiner et al 2006 did not referenced their diagnostic criteria for chronic pain and six included studies (Dick et al 2002 and 2008, DiStefano et al 1995, Grisart et al 2001, Ho Kim et al 2012, Lee et al 2010, Verdejo-Garcia et al 2009, Walitt et al 2008) did not screen controls to rule out the pre-existing cognitive deficits. These problems raise the risk of false inclusion. However all studies in this meta-analysis screened and excluded the patients that had pre-existing psychiatric or general medical conditions that would affect cognition. None of the included studies reported that their outcome assessors were blinded to group, which raises the risk of reporting and outcome bias. However, as reported previously, blinding in these studies would not be practically possible.

Future research:

Based on the risk of bias assessment, future studies should focus on the proper definition of the case and controls groups, chronic pain diagnostic criteria and screening of the control group for pain and psychiatric disorders. In the current studies, the sample sizes were small, thus, future studies should focus on larger patient samples. Also studies should be conducted to focus simultaneously on the imaging studies and EEG assessments.

Currently, MMSE and MoCA are less sensitive screening tools in detecting the milder forms of cognitive impairment in chronic pain patients thus cannot be recommended for use in clinical settings. In my opinion, future studies should focus on the development of new test batteries that are short and less time consuming but reliable and more focused on reporting of difficulties with simple speed, attention and memory.

In this meta-analysis cognitive impairments were not assessed according to the pain type and the widespread nature of the pain. In my opinion, future studies should focus on the pain type among different pain sub groups and localized versus the diffuse pain groups.

Conclusions

These results indicate that subjective complaints about cognitive deterioration, as reported by many chronic pain patients, can be consistently and objectively demonstrated with the help of standardized neuropsychological tests. Chronic pain was associated with poorer performances on many tests with Effect Sizes between about 1/3 to a full SD. Cognitive correlates of chronic pain were non-specific, with relative weaknesses in tests requiring speed, working memory, learning, executive functions, mental flexibility and a range of attention abilities. Based on this analysis, sustained attention and working memory are affected the most with larger effect size. Patients with chronic pain may perform worse on one construct but not on the other as obvious in WCST and Stroop tests.

Based on the results of this analysis, systematic assessment of basic neurocognitive functions is warranted in clinical practice. Careful and cautious interpretation of the results with proper definition of the case and control group is the key to reduce the threat to validity. Based on the literature review, it is hypothesized that impairments on neuropsychological tests is not solely dependent on psychological complaints. More research is needed to test non-verbal abilities, executive functions, and to control for estimated pre-morbid IQ and with larger sample sizes.

CHAPTER 5: RESTRICTED ANALYSIS

Restricted analysis was performed based on comparing the IQ between the patient and control group. Only five studies (Schmand et al 1998, chronic pain group of Suhr et al 2003, Walitt et al 2008 and Weiner et al 2006) had compared the patient and control group IQ. In all these five studies, the difference of the effect size between patient and control group was less than 0.5 SD. For restricted analysis, only the cognitive tests that two or more authors reported were included; this gave nine constructs. Based on this criteria, ROCF- Delayed recall, WCST- Preservative errors, WCST- No of categories, WAIS –Digit span forward, WAIS Digit span backward and WAIS digit span and PASAT, only one author reported those tests, thus, were excluded. All the subcomponents of the Test of Everyday Attention were excluded as Dick et al 2002 and Dick et al 2008 did not compared the patient and control IQ.

Table # 18 shows variable changes in the effect size of the neurocognitive test performance. It is hypothesized that the effects size in most of the constructs such as WAIS Digit symbol, Stroop Color, Stroop Word, Stroop Color-Word, RAVLT-Immediate recall and RAVLT delayed recognition increased. However the effects size decreased in TMT-A, TMT-B and RAVLT- delayed recall constructs. It is hypothesisized that performance on the neuropsychological tests does not solely depend on IQ and actually the effects size in some constructs increased when IQ was equated.

The weakness of the secondary analysis is that many studies and constructs were omitted. Some of the constructs had only one study left in the analysis, which does not fulfill the criteria for the meta-analysis. However the purpose of the secondary analysis was to assess the effect size in the construct after equating IQ. It is opined that future studies should compare pre-morbid IQ of the samples.

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Appendix

Literature search Strategy:

Ovid: Current Search History http://ovidsp.tx.ovid.com.libaccess.lib.mcmaster.ca/sp-3.10.0b/ovidweb.cgi

Wolters Kluwer Health | OvidSP

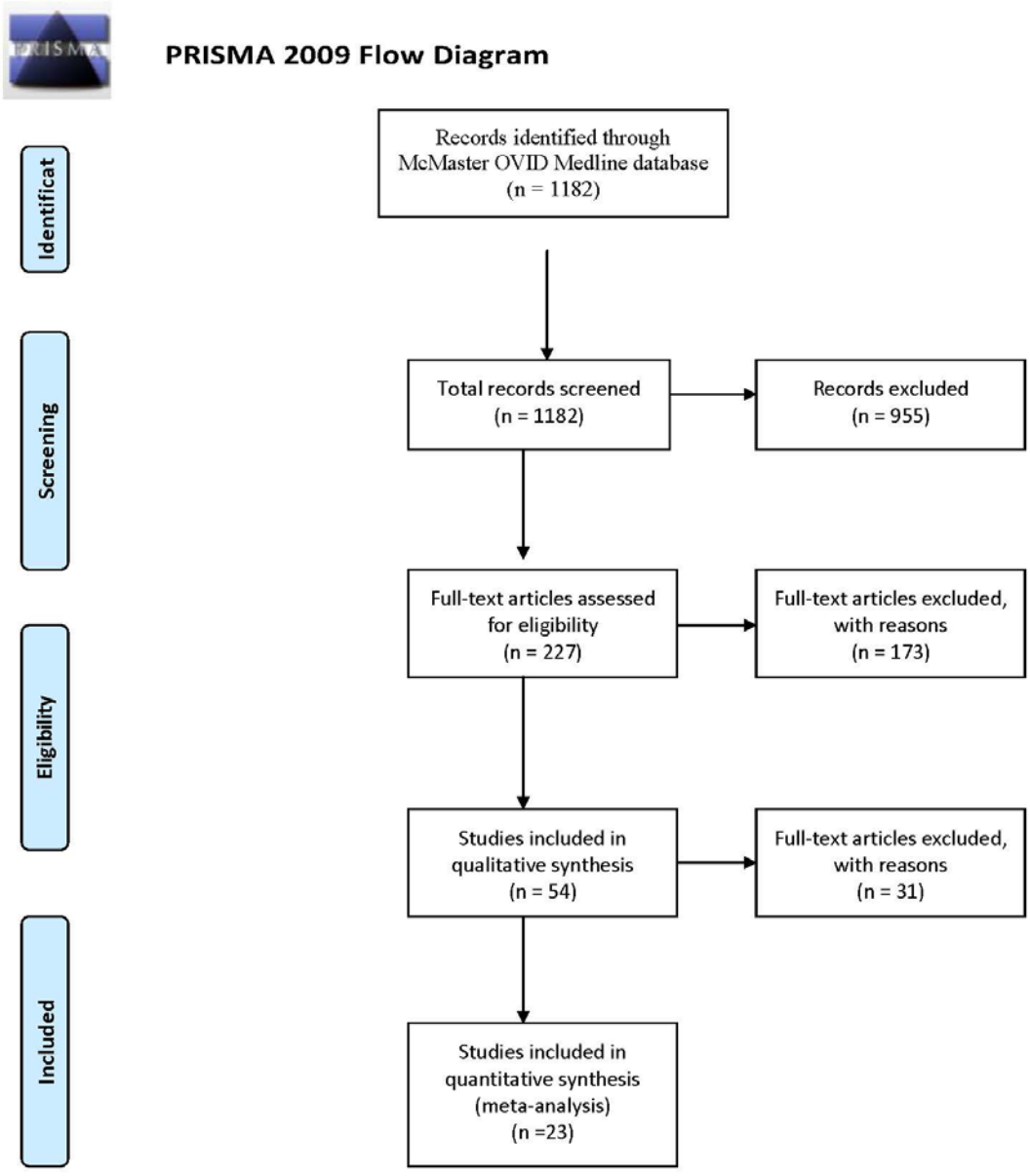
My Account | Support & Training | Help | Logoff

Search Journals Books Multimedia My Workspace

Ovid MEDLINE(R) 1946 to August Week 4 2013

#	Searches	Results	Search Type
1	Wechsler Scales/	5606	Advanced
2	Test of Everyday Attention.mp.	56	Advanced
3	Symbol Digit Modalities Test.mp.	265	Advanced
4	Rey Osterrieth Complex Figure Test.mp.	144	Advanced
5	Reaction time task.mp.	1901	Advanced
6	Working memory task.mp.	1708	Advanced
7	PASAT.mp.	277	Advanced
8	Number Connection Test.mp.	167	Advanced
9	Wechsler Scales/ or Wechsler memory scale.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	6172	Advanced
10	CVLT.mp.	377	Advanced
11	Wechsler Scales/ or WAIS.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]	6762	Advanced
12	Neuropsychological Tests/	69514	Advanced
13	Memory/ or Memory, Long-Term/ or Memory, Episodic/ or Memory, Short-Term/	69406	Advanced
14	mental competency/ or mental health/ or mental processes/ or cognition/ or awareness/ or cognitive dissonance/ or cognitive reserve/ or comprehension/ or consciousness/ or imagination/ or intuition/ or executive function/ or learning/ or psychomotor performance/	222360	Advanced
15	attention/ or reaction time/	128469	Advanced
16	memory/ or deja vu/ or memory, episodic/ or memory, long-term/ or memory, short-term/ or mental recall/ or "recognition (psychology)"/ or repetition priming/ or "retention (psychology)"/	100909	Advanced
17	executive function/ or higher nervous activity/	6063	Advanced
18	Cognitive interference.mp.	140	Advanced
19	Information-processing speed.mp.	606	Advanced
20	Physical Performance.mp.	4298	Advanced
21	Neuropsychological Performance.mp.	1541	Advanced
22	cognitive functions.mp.	8638	Advanced
23	Neuropsychological Tests/ or Attention/ or Memory/ or Effortful processing.mp. or Mental Recall/ or Cognition/ or Reaction Time/	279479	Advanced
24	Distraction.mp.	10531	Advanced
25	whiplash injury.mp.	986	Advanced
26	Catastrophizing.mp. or Catastrophization/	1303	Advanced
27	Fear.mp. or Fear/	46818	Advanced
28	Pain Measurement/	62031	Advanced
29	Complex Regional Pain Syndromes/ or Pelvic Girdle Pain/ or Low Back Pain/ or Pelvic Pain/ or Flank Pain/ or Back Pain/ or Musculoskeletal Pain/ or Neck Pain/ or Nociceptive Pain/ or Facial Pain/ or Chest Pain/ or Abdominal Pain/ or Shoulder Pain/ or Myofascial Pain Syndromes/ or Pain/ or Visceral Pain/ or Chronic Pain/	178483	Advanced
30	fibromyalgia.mp. or Fibromyalgia/	7415	Advanced
31	25 or 26 or 27 or 28 or 29 or 30	262222	Advanced
32	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24	423626	Advanced
33	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12	77822	Advanced
34	31 and 32 and 33	1393	Advanced
35	limit 34 to (english language and humans)	1182	Advanced

English | Français | Deutsch | 日本語 | 繁體中文 | Español | 简体中文 | 한국어



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.

Total records screened (n = 1182)							
neurological	TBI/ dementia	Psychological	Review/ meta-analysis, case reports	Medication effects	Animal studies	Other	Total pain
141	82	231	49	131	9	310	227

Full-text articles assessed for eligibility (n = 227)							
Psychological/ Malingering	Affect on living/ desensitization/ somatosensory functions/ systemic effects	Treatment	Imaging/ structural/ EVP/ EEG	Duplicate	Comparison of pain vs. Pain or two test	Others	Selected
44	28	9	43	28	12	9	54

Studies included in qualitative synthesis (n = 54)		
No control	Data problem/ Correlational studies	selected
15	16	23

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE
CASE CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Selection

1) Is the case definition adequate?
   a) yes, with independent validation ☐
   b) yes, eg record linkage or based on self reports
   c) no description

2) Representativeness of the cases
   a) consecutive or obviously representative series of cases ☐
   b) potential for selection biases or not stated

3) Selection of Controls
   a) community controls ☐
   b) hospital controls
   c) no description

4) Definition of Controls
   a) no history of disease (endpoint) ☐
   b) no description of source

Comparability

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for _____ (Select the most important factor.) ☐
   b) study controls for any additional factor ☐ (This criteria could be modified to indicate specific control for a second important factor.)

Exposure

1) Ascertainment of exposure
   a) secure record (eg surgical records) ☐
   b) structured interview where blind to case/control status ☐
   c) interview not blinded to case/control status
   d) written self report or medical record only
   e) no description

2) Same method of ascertainment for cases and controls
   a) yes ☐
   b) no

3) Non-Response rate
   a) same rate for both groups ☐
   b) non respondents described
   c) rate different and no designation

CODING MANUAL FOR CASE-CONTROL STUDIES

SELECTION

1) Is the Case Definition Adequate?

a) Requires some independent validation (e.g. >1 person/record/time/process to extract information, or reference to primary record source such as x-rays or medical/hospital records) ☆
b) Record linkage (e.g. ICD codes in database) or self-report with no reference to primary record
c) No description

2) Representativeness of the Cases

a) All eligible cases with outcome of interest over a defined period of time, all cases in a defined catchment area, all cases in a defined hospital or clinic, group of hospitals, health maintenance organisation, or an appropriate sample of those cases (e.g. random sample) ☆
b) Not satisfying requirements in part (a), or not stated.

3) Selection of Controls

This item assesses whether the control series used in the study is derived from the same population as the cases and essentially would have been cases had the outcome been present.

a) Community controls (i.e. same community as cases and would be cases if had outcome) ☆
b) Hospital controls, within same community as cases (i.e. not another city) but derived from a hospitalised population
c) No description

4) Definition of Controls

a) If cases are first occurrence of outcome, then it must explicitly state that controls have no history of this outcome. If cases have new (not necessarily first) occurrence of outcome, then controls with previous occurrences of outcome of interest should not be excluded. ☆
b) No mention of history of outcome

COMPARABILITY

1) Comparability of Cases and Controls on the Basis of the Design or Analysis

A maximum of 2 stars can be allotted in this category

Either cases or controls must be matched in the design and/or confounders must be adjusted for in the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability. Note: If the odds ratio for the exposure of interest is adjusted for the confounders listed, then the groups will be considered to be comparable on each variable used in the adjustment.

There may be multiple ratings for this item for different categories of exposure (e.g. ever vs. never, current vs. previous or never)

Age =☆ , Other controlled factors = ☆

EXPOSURE

1) **Ascertainment of Exposure**

   Allocation of stars as per rating sheet

2) **Non-Response Rate**

   Allocation of stars as per rating sheet

Risk of Bias Assessment # 1

	Selection				Comparability	Exposure		
	Case definition	Case represent	Control selection	Control definition	Comparability of case and control (design) 2stars	Ascertainment of exposure	Method of ascertainment	No response
Bosma 2003								
CaNovas 2009								
Dick 2002								
Dick 2008								
DiStefano 1995								
Gimse 1997								
Grace 1999								
Grisart 2001								
Ho Kim 2012								
Landro 1997								
Leavitt 2006								
Lee 2010								
Oosterman 2011								
Oosterman 2012								
Schmand 1998								
Shur 2003								
Sjogren 2005								
Verdejo Garcia 2012								
Walitt 2008								
Weiner 2006								

Risk Of Bias Assessment #2

Risk of Bias Assessment						**(New Castle Ottawa Guidelines)**			
Authors	**Selection**				**Comparability**	**Exposure**			**Total stars in study**
	Case definition	**Case representation**	**Control selection**	**Control definition**	**Comparability**	**Ascertainment**	**Method of ascertainment**	**No response**	
Bosma 2002	*	*	-	-	-	-	*	*	**4**
Ca Novas 2009	*	*	*	*	*	-	*	*	**7**
Dick 2002	*	*	*	*	*	-	*	*	**7**
Dick 2008	*	*	*	*	*	-	*	*	**7**
DiStefano 1995	-	*	*	*	*	-	*	*	**5**
Gimse 1997	*	*	*	-	*	-	*	*	**6**
Grace 1999	*	*	*	*	*	-	*	*	**7**
Grisart 2001	*	*	*	*	-	-	*	*	**5**
Ho Kim 2012	*	-	*	*	*	-	*	*	**6**
Landro 1997	*	*	*	*	-	-	*	*	**6**
Leavitt 2006	*	*	-	-	*	-	*	*	**5**
Lee 2010	*	*	*	*	*	-	*	*	**7**
Oosterman 2011	*	*	*	*	**	-	*	*	**8**
Oosterman 2012	*	*	*	*	**	-	*	*	**8**
Schmand 1998	*	*	*	-	-	-	*	*	**5**
Suhr 2003	*	*	*	*	-	-	*	*	**5**

Sjogren 2005	*	*	*	-	-	-	*	*	**5**
Verdejo Garcia 2012	*	-	*	*	*	-	*	*	**6**
Walitt 2008	*	*	*	*	-	-	*	*	**6**
Weiner 2006	*	*	*	*	-	-	*	*	**6**
Total stars in domain	**19**	**18**	**18**	**15**	**13/40**	**0**	**20**	**20**	
Percentage	**95%**	**90%**	**90%**	**75%**	40% do not meet the criteria for compara bility		**100%**	**100 %**	

Excel data sheet (Main Analysis):

		Mean		SD		Pooled				P-value	sample size		
Cognitve measure	Pain measure	patient	control	patient	Control	SD	Effect		% weight	patient	patient	control	Reference
Corsi Block- spatial forward	Fibromyalgia Impact Questionnaire (FIQ)	4.86	5.26	1.12	0.46	0.856154	-0.467206	-0.3504	-0.4	0.21	15	15	Ca Novas et al 2009
Corsi Block- spatial forward	Fibromyalgia Impact Questionnaire (FIQ)	6	6.2	1	1	1	-0.2	-0.2	-0.2	0.36	23	24	Ho Kim et al 2012
Corsi Block- spatial forward	self rating scale	11	11.5	1.7	1.4	1.557241	-0.321081	-0.32108	-0.5		21	21	DiStefano et al 1995
Corsi Block- spatial forward	self rating scale	11	11.2	1.5	1.4	1.450862	-0.137849	-0.13785	-0.2		21	21	DiStefano et al 1995
ROCF- immediate	pdiagram	33.4	33.5	4.2	4.4	4.366171	-0.022903	-0.0229	-0.1	0.12	266	1273	Lee et al 2010
ROCF- immediate		46.9	66.3	29.4	25.4	27.50668	-0.705283	-0.70702	-19.4	0.05	31	30	Bosma et al 2002
ROCF- immediate recall	Fibromyalgia Impact Questionnaire (FIQ)	16	24.3	7.4	5.6	6.542171	-1.268692	-1.26869	-8.3	0.001	23	24	Ho Kim et al 2012
ROCF- delayed	pdiagram	16.6	17.1	6.3	6.6	6.549256	-0.076345	-0.07634	-0.5	0.29	266	1273	Lee et al 2010
ROCF- delayed recall	Fibromyalgia Impact Questionnaire (FIQ)	16.5	23.8	7.3	5.5	6.443136	-1.132989	-1.13299	-7.3	0.001	23	24	Ho Kim et al 2012
ROCF- delayed recall		32.2	45.2	22	29.9	26.18263	-0.496512	-0.49401	-13		31	30	Bosma et al 2002
ROCF- delay recall	McGill Pain Questionnaire	15.6	16.8	5.8	4.3	5.140595	-0.233436	-0.23344	-1.2	NS	23	21	Shur et al 2003
ROCF- delay recall	McGill Pain Questionnaire	16.1	16.8	5.8	4.3	5.123452	-0.136627	-0.13663	-0.7	NS	22	21	Shur et al 2003
WCST-% perseverative errors (Tsc	WHYMPI	38.4	36.53	15.89	10.71	13.54984	0.138009	-0.14465	1.87	0.54	36	36	Verdejo-Garcia et al 2009
WCST- percent perseverative respo	McGill Pain Questionnaire	13.3	13.6	8.3	10.3	9.306142	-0.032237	0.03224	-0.3	NS	23	21	Shur et al 2003
WCST- percent perseverative respo	McGill Pain Questionnaire	18.6	13.6	15.9	10.3	13.46251	0.3714017	-0.3714	5	NS	22	21	Shur et al 2003
WCST- No of categories	WHYMPI	3.08	4.36	2.14	1.71	1.936969	-0.660826	-0.66083	-1.28	0.007	36	36	Verdejo-Garcia et al 2009
WCST- Number of categories comp	McGill Pain Questionnaire	5.3	4.9	1.3	1.9	1.61378	0.2478653	0.24787	0.4	NS	23	21	Shur et al 2003
WCST- Number of categories comp	McGill Pain Questionnaire	4.4	4.9	2.1	1.9	2.004933	-0.249385	-0.24938	-0.5	NS	22	21	Shur et al 2003
WAIS- Digit symbol (DS)	McGill Pain Questionnaire	10.2	11.8	2.5	2.3	2.406836	-0.664773	-0.66477	-1.6	NS	23	21	Shur et al 2003
WAIS- Digit symbol (DS)	McGill Pain Questionnaire	10.5	11.8	2.5	2.3	2.404518	-0.540649	-0.54065	-1.3	NS	22	21	Shur et al 2003
WAIS- Digit symbol (DS)	pdiagram	25.9	28.3	8.4	8.7	8.649018	-0.277488	-0.27749	-2.4	0.001	266	1273	Lee et al 2010
WAIS- Digit symbol (DS)	pain severity scale of MPI-PS	51.93	55.8	12.6	7.94	10.53099	-0.367487	-0.3675	-3.87	0.08	30	30	Grace 1999
WAIS digit symbol		57.9	64	10.3	8.8	9.708863	-0.628292	-0.61743	-6.1	0.0001	65	46	Schmand et al 1998
WAIS- Digit span forward	visual analog scale (VAS)	6	6.4	1.3	0.7	1.091989	-0.366304	-0.3663	-0.4	NS	25	18	Landro et al 1997
WAIS- Digit span- forward	Fibromyalgia Impact Questionnaire (FIQ)	5.2	5	1.14	0.84	1.001299	0.1997405	0.19974	0.2	0.59	15	15	Ca Novas et al 2009
WAIS- Digit span- forward	Fibromyalgia Impact Questionnaire (FIQ)	8.4	9	2.5	2.6	2.551601	-0.235147	-0.23515	-0.6	0.414	23	24	Ho Kim et al 2012
WAIS- Digit span backward	visual analog scale (VAS)	5.5	6.2	2	1.6	1.817278	-0.385191	-0.38519	-0.7	0.05	34	32	Oosterman et al 2011
WAIS- Digit span backward	visual analog scale (VAS)	4.5	5.1	1.2	0.8	1.052755	-0.569933	-0.56993	-0.6	NS	25	18	Landro et al 1997
WAIS- Digits span- Backward	Fibromyalgia Impact Questionnaire (FIQ)	3.93	4.33	1.16	0.97	1.069229	-0.374101	-0.3741	-0.4	0.32	15	15	Ca Novas et al 2009
WAIS- Digits span- Backward	Fibromyalgia Impact Questionnaire (FIQ)	6.4	7	2.4	2.1	2.251666	-0.266469	-0.26647	-0.6	0.39	23	24	Ho Kim et al 2012
WAIS- Digit span	self rating scale	10.2	10.5	2.2	1.9	2.05548	-0.145951	-0.14595	-0.3		21	21	DiStefano et al 1995
WAIS- Digit span	self rating scale	10.6	11.2	2.4	2	2.209072	-0.271607	-0.27161	-0.6		21	21	DiStefano et al 1995
WAIS- Digit span		10.2	10.3	2.4	2.8	2.607681	-0.038348	-0.03835	-0.1		35	35	Leavitt et al 2007
WAIS- Digit span	McGill Pain Questionnaire	10.2	11.6	2.4	2.5	2.448129	-0.571865	-0.57187	-1.4	NS	23	21	Shur et al 2003
WAIS- Digit span	McGill Pain Questionnaire	11.3	11.6	3.3	2.5	2.937105	-0.102141	-0.10214	-0.3	NS	22	21	Shur et al 2003
TMT- A		*55.6*	*52*	*31.3*	*27.6*	*29.5393*	*0.121871*	*0.12187*	*3.6*	*NS*	*31*	*30*	*Bosma et al 2002*
TMT- A	Pain Catastrophizing	40.3	31.7	15.5	9.9	13.09017	0.6569816	-0.65698	8.6	0.01	34	32	Oosterman 2012
TMT- A	Fibromyalgia Impact Questionnaire (FIQ)	54.6	51.5	14.3	10.2	12.42035	0.2495905	-0.24959	3.1		27	27	Walitt et al 2008
TMT- A	Fibromyalgia Impact Questionnaire (FIQ)	50	51.5	8.8	10.2	9.670766	-0.155107	0.15511	-1.5		18	27	Walitt et al 2008
TMT- A	No pain measurment tool	31.91	29.55	12.78	6.95	10.10665	0.2335096	-0.23603	2.36	0.369	23	26	Gimse et al 1997
TMT-A	self rating scale	26.2	22	9.9	13.3	11.72391	0.3582423	-0.35824	4.2		21	21	DiStefano et al 1995
TMT-A	self rating scale	26.4	21.5	11.2	10	10.61697	0.4615254	0.46153	4.9		21	21	DiStefano et al 1995
TMT-A	McGill Pain Questionnaire	28	24.7	9.3	6.9	8.244739	0.4002553	-0.43664	3.3	NS	23	21	Shur et al 2003
TMT-A	McGill Pain Questionnaire	27.7	24.7	10.3	6.9	8.806996	0.3406383	-0.34064	3	NS	22	21	Shur et al 2003
TMT-A		35	30	13	10	11.85385	0.4218039	-0.41021	5	0.001	65	46	Schmand et al 1998

TMTB	Fibromyalgia Impact Questionnaire (FIQ)	52.1	48.1	10.2	11.2	10.71168	0.3734243	-0.37342	4		27	27 Walitt et al 2008
TMTB	Fibromyalgia Impact Questionnaire (FIQ)	49.1	48.1	9.6	11.2	10.59636	0.0943721	-0.09437	1		18	27 Walitt et al 2008
TMT-B	self rating scale	77.9	61	23.8	21.3	22.58462	0.7482969	-0.7483	16.9		21	21 DiStefano et al 1995
TMT-B	self rating scale	86.5	63.8	33.7	39.4	36.66095	0.6191875	-0.61919	22.7		21	21 DiStefano et al 1995
TMT-B		69	60	23	22	22.59252	0.3983619	-0.39633	9	0.0001	65	46 Schmand et al 1998
TMT-B	Pain Catastrophizing	98	76.9	56.8	27.8	45.14282	0.4674054	-0.46741	21.1	NS	34	32 Oosterman 2012
TMT-B	McGill Pain Questionnaire	68.9	52.3	28.7	11.2	22.16281	0.7490026	-0.749	16.6	NS	23	21 Shur et al 2003
TMT-B	McGill Pain Questionnaire	72	52.3	36.1	11.2	26.99422	0.7297858	-0.72979	19.7	NS	22	21 Shur et al 2003
TMT- B		*58.8*	*65.5*	*28.2*	*26*	*27.1409*	*-0.24686*	*0.2472*	*-6.7*	*NS*	*31*	*30 Bozma et al 2002*
TMT- B	No pain measurment tool	79.09	66.36	40.74	21.63	32.02754	0.3974705	-0.39747	12.73	0.17	23	26 Gimse et al 1997
TMT- B	*MPQ SF*	*53.7*	*50.73*	*11.36*	*10.22*	*10.8104*	*0.274736*	*0.26297*	*2.97*	*0.019*	*163*	*160 Weiner et al 2006*
TEA- working memory	Numerical Rating Scale (NRS), McGill Pain Qu	18.53	21.8	5.37	4.33	4.877797	-0.670385	-0.67038	-3.27	0.006	30	30 Dick et al 2008
TEA- working memory	visual analog scale (VAS)	15	22.2	4.4	4.4	4.4	-1.636364	-1.63636	-7.2	0.005	20	20 Dick et al 2002
TEA- working memory	visual analog scale (VAS)	17.9	22.2	5.5	4.4	4.980462	-0.863374	-0.86337	-4.3	0.005	20	20 Dick et al 2002
TEA- working memory	visual analog scale (VAS)	18.5	22.2	4	4.4	4.204759	-0.879955	-0.87996	-3.7	NS	20	20 Dick et al 2002
TEA- switching attention	visual analog scale (VAS)	7.4	9.5	3.5	3.1	3.306055	-0.635198	-0.6352	-2.1	NS	20	20 Dick et al 2002
TEA- switching attention	visual analog scale (VAS)	9.2	9.5	3.6	3.1	3.359315	-0.089304	-0.0893	-0.3	NS	20	20 Dick et al 2002
TEA- switching attention	visual analog scale (VAS)	7.6	9.5	2.9	3.1	3.001666	-0.632982	-0.63298	-1.9	NS	20	20 Dick et al 2002
TEA- sustained attention	Numerical Rating Scale (NRS), McGill Pain Qu	27.07	29.7	4.33	3.53	3.950304	-0.665772	-0.66577	-2.63	0.005	30	30 Dick et al 2008
TEA- Sustained attention	visual analog scale (VAS)	23.8	29.3	4.6	3.7	4.174326	-1.317578	-1.31758	-5.5	0.005	20	20 Dick et al 2002
TEA- Sustained attention	visual analog scale (VAS)	27.4	29.3	3.5	3.7	3.601389	-0.527574	-0.52757	-1.9	NS	20	20 Dick et al 2002
TEA- Sustained attention	visual analog scale (VAS)	25.6	29.3	5.9	3.7	4.924429	-0.751356	-0.75136	-3.7	NS	20	20 Dick et al 2002
TEA- selective attention	Numerical Rating Scale (NRS), McGill Pain Qu	29.4	32.7	6.08	5.98	6.030207	-0.547245	-0.54724	-3.3	0.005	30	30 Dick et al 2008
TEA- selective attention	visual analog scale (VAS)	24.8	33.4	6.1	8	7.113719	-1.208932	-1.20893	-8.6	0.005	20	20 Dick et al 2002
TEA- selective attention	visual analog scale (VAS)	25.2	33.4	6.6	8	7.333485	-1.118159	-1.11816	-8.2	0.005	20	20 Dick et al 2002
TEA- selective attention	visual analog scale (VAS)	25.1	33.4	10.1	8	9.110708	-0.911016	-0.91102	-8.3	0.005	20	20 Dick et al 2002
Stroop- C	Pain Catastrophizing	61.8	59.2	10.2	9.2	9.72847	0.2672568	-0.26726	2.6	NS	34	32 Oosterman 2012
stroop- C		47	41	13	6	11.3853	0.5269955	-0.527	6	0.001	108	46 Schmand et al 1998
Stroop- C	*Fibromyalgia Impact Questionnaire (FIQ)*	*50.4*	*49.7*	*7.2*	*7.9*	*7.35811*	*0.092616*	*0.0926*	*0.7*		*27*	*27 Walitt et al 2008*
Stroop- C	*Fibromyalgia Impact Questionnaire (FIQ)*	*50.4*	*47.4*	*7.2*	*7.3*	*7.26063*	*0.413187*	*-0.4144*	*3*		*18*	*27 Walitt et al 2008*
Stroop- word	*Pain Catastrophizing*	*49*	*47.4*	*10*	*8.3*	*9.21581*	*0.173615*	*0.17462*	*1.6*	*NS*	*34*	*32 Oosterman 2012*
Stroop- word	*Fibromyalgia Impact Questionnaire (FIQ)*	*52.3*	*50.9*	*8.5*	*8.6*	*8.55015*	*0.16374*	*-0.1637*	*1.4*		*27*	*27 Walitt et al 2008*
Stroop- word	*Fibromyalgia Impact Questionnaire (FIQ)*	*52.3*	*49.1*	*8.5*	*6.9*	*7.57307*	*0.42255*	*-0.4047*	*3.2*		*18*	*27 Walitt et al 2008*
Stroop card W		63	54	17	7	14.76304	0.6096305	-0.60963	9	0.0001	108	46 Schmand et al 1998
Stroop card C/W		99	86	30	17	25.45098	0.5107859	-0.48478	13	0.0001	65	46 Schmand et al 1998
Stroop- Color-word	Fibromyalgia Impact Questionnaire (FIQ)	54.1	50	9.5	7.2	8.42882	0.4864264	-0.48643	4.1	0.005	27	27 Walitt et al 2008
Stroop- Color-word	Fibromyalgia Impact Questionnaire (FIQ)	52.9	50	9.3	7.2	8.095606	0.358219	-0.40057	2.9	0.05	18	27 Walitt et al 2008
Stroop- C/W card	Pain Catastrophizing	99.4	97.7	21.7	24.6	23.1501	0.0734338	-0.07343	1.7	NS	34	32 Oosterman 2012
RAVLT- immediate recall	pain severity scale of MPI-PS	53.57	55.2	9.09	6.9	8.069638	-0.201992	-0.20199	-1.63	0.22	30	30 Grace et al 1999
RAVLT- immediate recall	McGill Pain Questionnaire	9.7	11.1	2.9	2.7	2.80654	-0.498835	-0.49883	-1.4	NS	23	21 Shur et al 2003
RAVLT- immediate recall	McGill Pain Questionnaire	10.5	11.1	3.2	2.7	2.966644	-0.202249	-0.20225	-0.6	NS	22	21 Shur et al 2003
RAVLT- immediate recall	Fibromyalgia Impact Questionnaire (FIQ)	55.9	60.9	9.6	8.6	9.102625	-0.549292	-0.54929	-5	0.65	23	24 Ho Kim et al 2012
RAVLT- immediate recall	No pain measurment tool	11.65	13.35	2.46	1.37	1.957298	-0.868544	-0.86854	-1.7	0.016	23	26 Gimse et al 1997
RAVLT immediate recall		48.6	54.9	8.8	8.2	8.626718	-0.730289	-0.73029	-6.3	0.0001	108	46 Schmand et al 1998
RAVLT delayed recall		10.6	12.3	2.8	2.5	2.714641	-0.626234	-0.62623	-1.7	0.0001	108	46 Schmand et al 1998
RAVLT- delayed recall	No pain measurment tool	-3.26	-1.43	2.16	1.85	2.001094	-0.9145	-0.9145	-1.83	0.007	23	26 Gimse et al 1997
RAVLT- delayed recall	Fibromyalgia Impact Questionnaire (FIQ)	11.7	13.4	2.5	1.6	2.089019	-0.813779	-0.81378	-1.7	0.011	23	24 Ho Kim et al 2012
RAVLT-delayed recall	McGill Pain Questionnaire	9.2	10.7	2.9	2.9	2.9	-0.517241	-0.51724	-1.5	NS	23	21 Shur et al 2003

RAVLT-delayed recall	McGill Pain Questionnaire	9.9	10.7	3.3	2.9	3.111309	-0.257126	-0.25713	-0.8 NS	22	21 Shur et al 2003
RAVLT- delayed recognition		28.4	29.7	2.7	0.9	2.317667	-0.560909	-0.56091	-1.3 0.0001	108	46 Schmand et al 1998
RAVLT-delayed recogition	*McGill Pain Questionnaire*	*13.5*	*14.9*	*1.4*	*4.8*	*3.46383*	*-0.404177*	*0.38826*	*-1.4 NS*	*23*	*21 Shur et al 2003*
RAVLT-delayed recogition	*McGill Pain Questionnaire*	*13.5*	*13.5*	*1.4*	*4.6*	*3.36539*	*0*	*0.40766*	*0 NS*	*22*	*21 Shur et al 2003*
PASAT	pain severity scale of MPI-PS	69.07	82.6	22.38	22.22	22.30014	-0.606723	-0.60672	-13.53 0.01	30	30 Grace et al 1999
PASAT	*self rating scale*	*7.1*	*14.4*	*8.4*	*4.7*	*6.80625*	*-1.072544*	*-1.0725*	*-7.3 0.001*	*21*	*21 DiStefano et al 1995*
PASAT	*self rating scale*	*7.7*	*14.1*	*7.2*	*4.9*	*6.15833*	*-1.039243*	*-1.0392*	*-6.4 0.002*	*21*	*21 DiStefano et al 1995*
PASAT		3	3.7	3.1	2	2.617736	-0.267407	-0.26741	-0.7 NS	31	30 Bosma et al 2002
PASAT	McGill Pain Questionnaire	37.3	43.7	12.7	10.4	11.66148	-0.548816	-0.54882	-6.4 NS	23	21 Shur et al 2003
PASAT	McGill Pain Questionnaire	41.6	43.7	14.4	10.4	12.60832	-0.166557	-0.16656	-2.1 NS	22	21 Shur et al 2003
PASAT	visual analog scale (VAS)	32.3	33.9	12.7	8.1	11.04049	-0.144921	-0.14492	-1.6 NS	91	64 Sjogren et al 2005
PASAT		5.2	7.1	2.5	2.8	2.654242	-0.715835	-0.71584	-1.9 0.01	35	35 Leavitt et al 2007
PASAT	No pain measurment tool	43.09	44.35	9.16	7.23	8.19022	-0.153842	-0.15384	-1.26 0.66	23	26 Gimse et al 1997

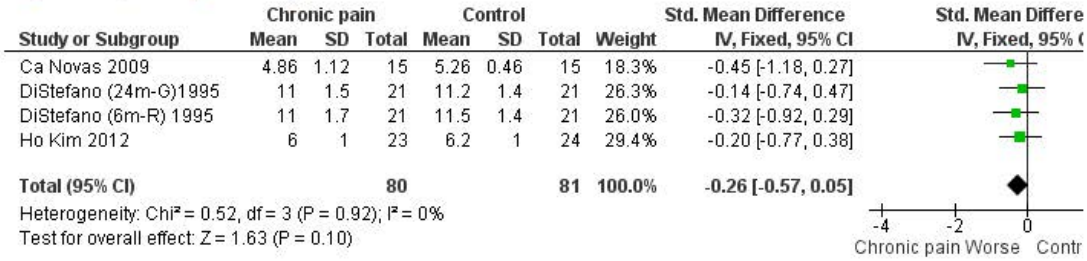
Excel Sheet (Restricted Analysis):

Cognitve measure	Pain measure	Mean patient	Mean control	SD patient	SD Control	Pooled SD	Effect		% weight	P-value patient	sample size patient	sample size control	Reference
WAIS- Digit symbol (DS)	McGill Pain Questionnaire	10.5	11.8	2.5	2.3	2.404518	-0.540649	-0.54065	-1.3	NS	22		21 Shur et al 2003
WAIS digit symbol		57.9	64	10.3	8.8	9.708863	-0.628292	-0.61743	-6.1	0.0001	65		46 Schmand et al 1998
TMT- A	Fibromyalgia Impact Questionnaire (FIQ)	54.6	51.5	14.3	10.2	12.42035	0.2495905	-0.24959	3.1		27		27 Walitt et al 2008
TMT- A	Fibromyalgia Impact Questionnaire (FIQ)	50	51.5	8.8	10.2	9.670766	-0.155107	0.155107	-1.5		18		27 Walitt et al 2008
TMT-A	McGill Pain Questionnaire	27.7	24.7	10.3	6.9	8.806996	0.3406383	-0.34064	3	NS	22		21 Shur et al 2003
TMT-A		35	30	13	10	11.85385	0.4218039	-0.41021	5	0.001	65		46 Schmand et al 1998
TMTB	Fibromyalgia Impact Questionnaire (FIQ)	52.1	48.1	10.2	11.2	10.71168	0.3734243	-0.37342	4		27		27 Walitt et al 2008
TMTB	Fibromyalgia Impact Questionnaire (FIQ)	49.1	48.1	9.6	11.2	10.59636	0.0943721	-0.09437	1		18		27 Walitt et al 2008
TMT-B		69	60	23	22	22.59252	0.3983619	-0.39633	9	0.0001	65		46 Schmand et al 1998
TMT-B	McGill Pain Questionnaire	72	52.3	36.1	11.2	26.99422	0.7297858	-0.72979	19.7	NS	22		21 Shur et al 2003
TMT- B	*MPQ-SF*	*53.7*	*50.73*	*11.36*	*10.22*	*10.81035*	*0.2747364*	*0.26297*	*2.97*	*0.019*	*163*	*160*	Weiner et al 2006
Stroop- C		47	41	13	6	11.3853	0.5269955	-0.527	6	0.001	108		46 Schmand et al 1998
Stroop- C	*Fibromyalgia Impact Questionnaire (FIQ)*	*50.4*	*49.7*	*7.2*	*7.9*	*7.558108*	*0.0926158*	*-0.09262*	*0.7*		*27*		27 Walitt et al 2008
Stroop- C	*Fibromyalgia Impact Questionnaire (FIQ)*	*50.4*	*47.4*	*7.2*	*7.3*	*7.26063*	*0.4131873*	*-0.41438*	*3*		*18*		27 Walitt et al 2008
Stroop- word	*Fibromyalgia Impact Questionnaire (FIQ)*	*52.3*	*50.9*	*8.5*	*8.6*	*8.550145*	*0.1637399*	*-0.16374*	*1.4*		*27*		27 Walitt et al 2008
Stroop- word	*Fibromyalgia Impact Questionnaire (FIQ)*	*52.3*	*49.1*	*8.5*	*6.9*	*7.57307*	*0.4225499*	*-0.40474*	*3.2*		*18*		27 Walitt et al 2008
Stroop card W		63	54	17	7	14.76304	0.6096305	-0.60963	9	0.0001	108		46 Schmand et al 1998
Stroop card C/W		99	86	30	17	25.45098	0.5107859	-0.48478	13	0.0001	65		46 Schmand et al 1998
Stroop- Color-word	Fibromyalgia Impact Questionnaire (FIQ)	54.1	50	9.5	7.2	8.42882	0.4864264	-0.48643	4.1	0.005	27		27 Walitt et al 2008
Stroop- Color-word	Fibromyalgia Impact Questionnaire (FIQ)	52.9	50	9.3	7.2	8.095606	0.358219	-0.40057	2.9	0.05	18		27 Walitt et al 2008
RAVLT- immediate recall	McGill Pain Questionnaire	10.5	11.1	3.2	2.7	2.966644	-0.202249	-0.20225	-0.6	NS	22		21 Shur et al 2003
RAVLT- immediate recall	Fibromyalgia Impact Questionnaire (FIQ)	55.9	60.9	9.6	8.6	9.102625	-0.549292	-0.54929	-5	0.65	23		24 Ho Kim et al 2012
RAVLT immediate recall		48.6	54.9	8.8	8.2	8.625718	-0.730289	-0.73029	-6.3	0.0001	108		46 Schmand et al 1998
RAVLT delayed recall		10.6	12.3	2.8	2.5	2.714641	-0.626234	-0.62623	-1.7	0.0001	108		46 Schmand et al 1998
RAVLT-delayed recall	McGill Pain Questionnaire	9.9	10.7	3.3	2.9	3.111309	-0.257126	-0.25713	-0.8	NS	22		21 Shur et al 2003
RAVLT- delayed recognition		28.4	29.7	2.7	0.9	2.317667	-0.560909	-0.56091	-1.3	0.0001	108		46 Schmand et al 1998
RAVLT-delayed recogition	*McGill Pain Questionnaire*	*13.5*	*14.9*	*1.4*	*4.8*	*3.463827*	*-0.404177*	*0.38826*	*-1.4*	*NS*	*23*		*21* Shur et al 2003
RAVLT-delayed recogition	*McGill Pain Questionnaire*	*13.5*	*13.5*	*1.4*	*4.6*	*3.365391*	*0*	*0.40765*	*0*	*NS*	*22*		*21* Shur et al 2003

REPORTING RESULTS

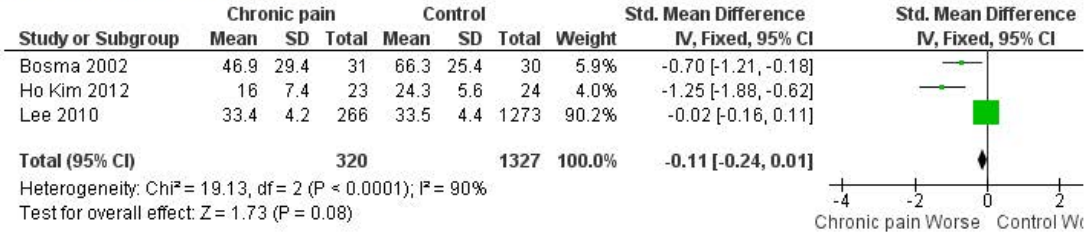
Figures

Figure 1 (Analysis 1.1)



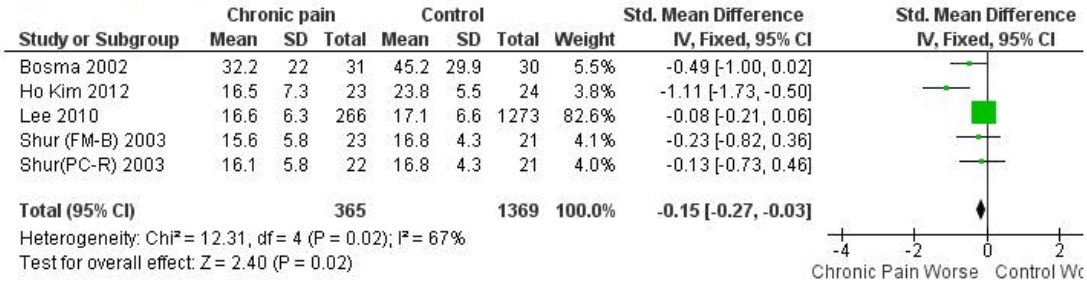
Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.1 Corsi Block- Spatial forward.

Figure 2 (Analysis 1.2)



Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.2 ROCF-immediate.

Figure 3 (Analysis 1.3)

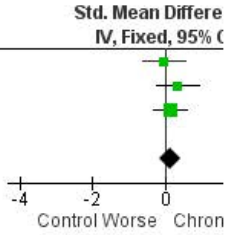


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.3 ROCF-delayed.

Figure 4 (Analysis 1.4)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Shur (FM-B) 2003	13.3	8.3	23	13.6	10.3	21	27.8%	-0.03 [-0.62, 0.56]
Shur(PC-R) 2003	18.6	15.9	22	13.6	10.3	21	26.7%	0.36 [-0.24, 0.97]
Verdejo- Garcia 2009	38.49	15.89	36	36.5	10.71	36	45.5%	0.15 [-0.32, 0.61]
Total (95% CI)			**81**			**78**	**100.0%**	**0.15 [-0.16, 0.47]**

Heterogeneity: Chi² = 0.85, df = 2 (P = 0.65); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

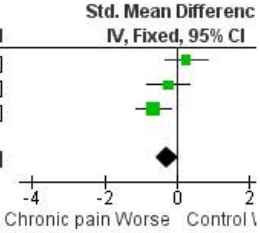


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.4 WCST-perservative errors.

Figure 5 (Analysis 1.5)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Shur (FM-B) 2003	5.3	1.3	23	4.9	1.9	21	28.2%	0.24 [-0.35, 0.84]
Shur(PC-R) 2003	4.4	2.1	22	4.9	1.9	21	27.6%	-0.24 [-0.85, 0.36]
Verdejo- Garcia 2009	3.08	2.14	36	4.36	1.71	36	44.2%	-0.65 [-1.13, -0.18]
Total (95% CI)			**81**			**78**	**100.0%**	**-0.29 [-0.60, 0.03]**

Heterogeneity: Chi² = 5.37, df = 2 (P = 0.07); I² = 63%
Test for overall effect: Z = 1.79 (P = 0.07)

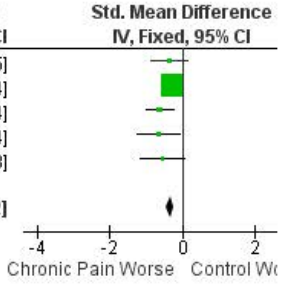


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.5 WCST No of categories.

Figure 6 (Analysis 1.6)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Grace 1999	51.93	12.6	30	55.8	7.94	30	5.3%	-0.36 [-0.87, 0.15]
Lee 2010	25.9	8.4	266	28.3	8.7	1273	78.2%	-0.28 [-0.41, -0.14]
Schmand 1998	57.9	10.3	65	64	8.8	46	9.2%	-0.62 [-1.01, -0.24]
Shur (FM-B) 2003	10.2	2.5	23	11.8	2.3	21	3.7%	-0.65 [-1.26, -0.04]
Shur(PC-R) 2003	10.5	2.5	22	11.8	2.3	21	3.7%	-0.53 [-1.14, 0.08]
Total (95% CI)			**406**			**1391**	**100.0%**	**-0.34 [-0.45, -0.22]**

Heterogeneity: Chi² = 4.33, df = 4 (P = 0.36); I² = 8%
Test for overall effect: Z = 5.64 (P < 0.00001)



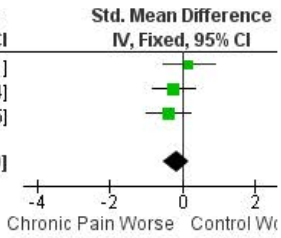
Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.6 WAIS-Digit symbol.

Chronic Pain versus Control for Cognitive impairment 28-Jun-2014

Figure 7 (Analysis 1.7)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ca Novas 2009	5.2	1.14	15	5	0.84	15	25.4%	0.19 [-0.52, 0.91]
Ho Kim 2012	8.4	2.5	23	9	2.6	24	39.7%	-0.23 [-0.81, 0.34]
Landro 1997	6	1.3	25	6.4	0.7	18	35.0%	-0.36 [-0.97, 0.25]
Total (95% CI)			**63**			**57**	**100.0%**	**-0.17 [-0.53, 0.19]**

Heterogeneity: Chi² = 1.40, df = 2 (P = 0.50); I² = 0%
Test for overall effect: Z = 0.91 (P = 0.36)

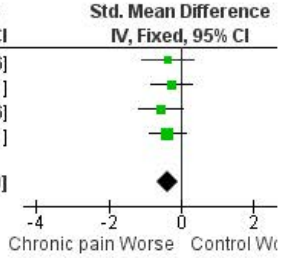


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.7 WAIS-Digit span forward.

Figure 8 (Analysis 1.8)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ca Novas 2009	3.93	1.16	15	4.33	0.97	15	16.3%	-0.36 [-1.09, 0.36]
Ho Kim 2012	6.4	2.4	23	7	2.1	24	25.7%	-0.26 [-0.84, 0.31]
Landro 1997	4.5	1.2	25	5.1	0.8	18	22.2%	-0.56 [-1.18, 0.06]
Oosterman 2011	5.5	2	34	6.2	1.6	32	35.8%	-0.38 [-0.87, 0.11]
Total (95% CI)			**97**			**89**	**100.0%**	**-0.39 [-0.68, -0.10]**

Heterogeneity: Chi² = 0.49, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 2.60 (P = 0.009)

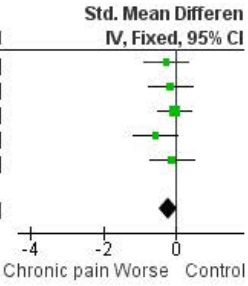


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.8 WAIS-Digit span backward.

Figure 9 (Analysis 1.9)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
DiStefano (24m-G)1995	10.6	2.4	21	11.2	2	21	17.4%	-0.27 [-0.87, 0.34]
DiStefano (6m-R) 1995	10.2	2.2	21	10.5	1.9	21	17.6%	-0.14 [-0.75, 0.46]
Leavitt 2007	10.2	2.4	35	10.3	2.8	35	29.3%	-0.04 [-0.51, 0.43]
Shur (FM-B) 2003	10.2	2.4	23	11.6	2.5	21	17.7%	-0.56 [-1.17, 0.04]
Shur(PC-R) 2003	11.3	3.3	22	11.6	2.5	21	18.0%	-0.10 [-0.70, 0.50]
Total (95% CI)			**122**			**119**	**100.0%**	**-0.20 [-0.45, 0.05]**

Heterogeneity: Chi² = 2.02, df = 4 (P = 0.73); I² = 0%
Test for overall effect: Z = 1.54 (P = 0.12)

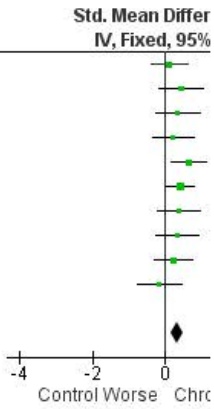


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.9 WAIS digit span.

Figure 10 (Analysis 1.10)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Bosma 2002	55.6	31.3	31	52	27.6	30	11.2%	0.12 [-0.38, 0.62]
DiStefano (24m-G)1995	26.4	11.2	21	21.5	10	21	7.5%	0.45 [-0.16, 1.07]
DiStefano (6m-R) 1995	26.2	9.9	21	22	13.3	21	7.6%	0.35 [-0.26, 0.96]
Gimse 1997	31.91	12.78	23	29.55	6.95	26	9.0%	0.23 [-0.33, 0.79]
Oosterman 2012	40.3	15.5	34	31.7	9.9	32	11.5%	0.65 [0.15, 1.15]
Schmand 1998	35	13	65	30	10	46	19.5%	0.42 [0.04, 0.80]
Shur (FM-B) 2003	28	9.3	23	24.7	6.9	21	7.9%	0.39 [-0.20, 0.99]
Shur(PC-R) 2003	27.7	10.3	22	24.7	6.9	21	7.8%	0.33 [-0.27, 0.94]
Walitt (FM)- 2008	54.6	14.3	27	51.5	10.2	27	9.9%	0.25 [-0.29, 0.78]
Walitt (MSK) 2008	50	8.8	18	51.5	10.2	27	8.0%	-0.15 [-0.75, 0.44]
Total (95% CI)			**285**			**272**	**100.0%**	**0.32 [0.15, 0.49]**

Heterogeneity: Chi² = 5.38, df = 9 (P = 0.80); I² = 0%
Test for overall effect: Z = 3.74 (P = 0.0002)

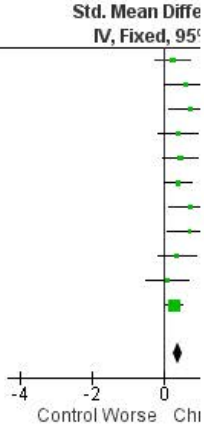


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.10 TMT-A.

Figure 11 (Analysis 1.11)

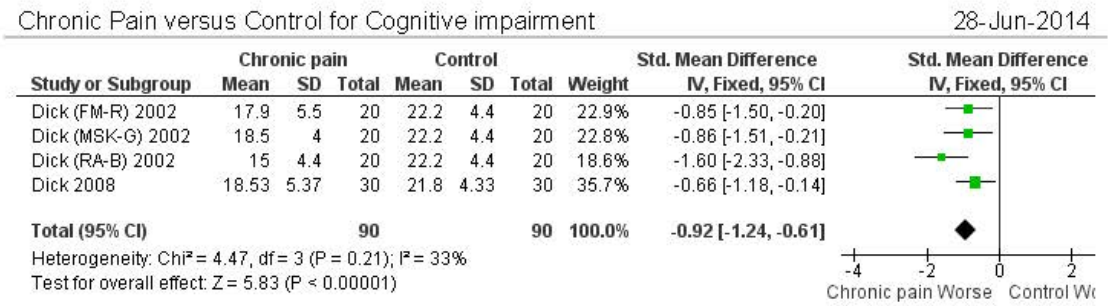
Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Bosma 2002	65.5	28.2	31	58.8	26	30	7.1%	0.24 [-0.26, 0.75]
DiStefano (24m-G)1995	86.5	33.7	21	63.8	39.4	21	4.7%	0.61 [-0.01, 1.23]
DiStefano (6m-R) 1995	77.9	23.8	21	61	21.3	21	4.6%	0.73 [0.11, 1.36]
Gimse 1997	79.09	40.74	23	66.36	21.63	26	5.6%	0.39 [-0.18, 0.96]
Oosterman 2012	98	56.8	34	76.9	27.8	32	7.5%	0.46 [-0.03, 0.95]
Schmand 1998	69	23	65	60	22	46	12.4%	0.40 [0.01, 0.78]
Shur (FM-B) 2003	68.9	28.7	23	52.3	11.2	21	4.8%	0.74 [0.12, 1.35]
Shur(PC-R) 2003	72	36.1	22	52.3	11.2	21	4.7%	0.72 [0.10, 1.34]
Walitt (FM)- 2008	52.1	10.2	27	48.1	11.2	27	6.2%	0.37 [-0.17, 0.91]
Walitt (MSK) 2008	49.1	9.6	18	48.1	11.2	27	5.1%	0.09 [-0.50, 0.69]
Weiner 2006	53.7	11.36	163	50.73	10.22	160	37.4%	0.27 [0.05, 0.49]
Total (95% CI)			**448**			**432**	**100.0%**	**0.38 [0.25, 0.52]**

Heterogeneity: Chi² = 6.35, df = 10 (P = 0.78); I² = 0%
Test for overall effect: Z = 5.61 (P < 0.00001)



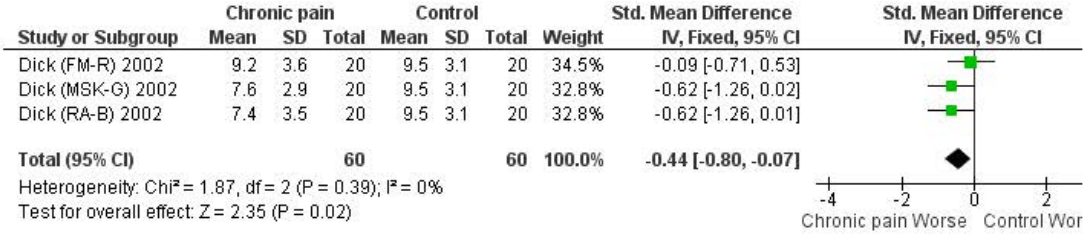
Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.11 TMT-B.

Figure 12 (Analysis 1.13)



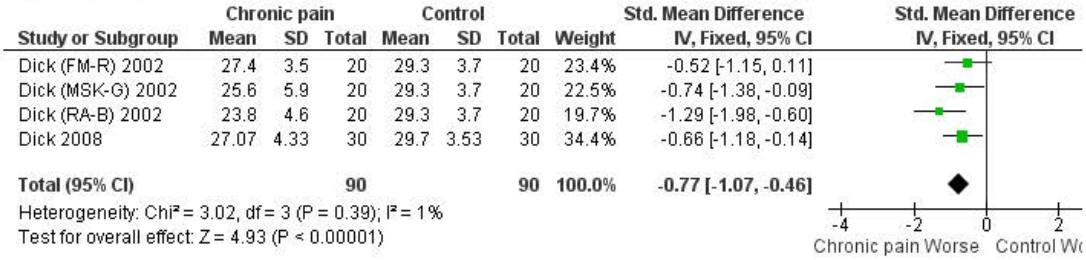
Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.13 TEA-Working memory.

Figure 13 (Analysis 1.14)



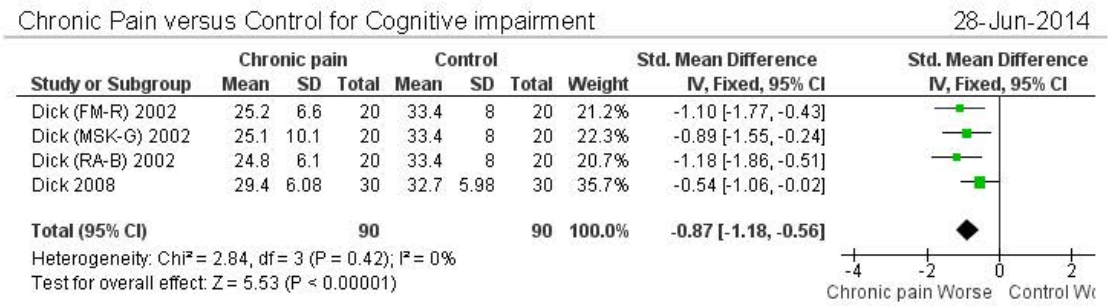
Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.14 TEA-Switching attention.

Figure 14 (Analysis 1.15)



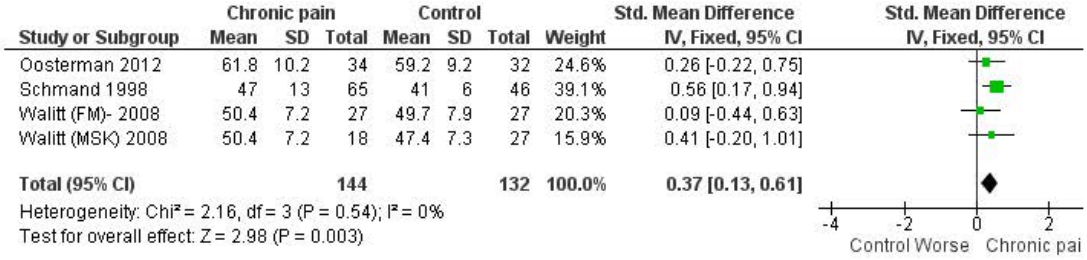
Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.15 TEA-Sustained Attention.

Figure 15 (Analysis 1.16)



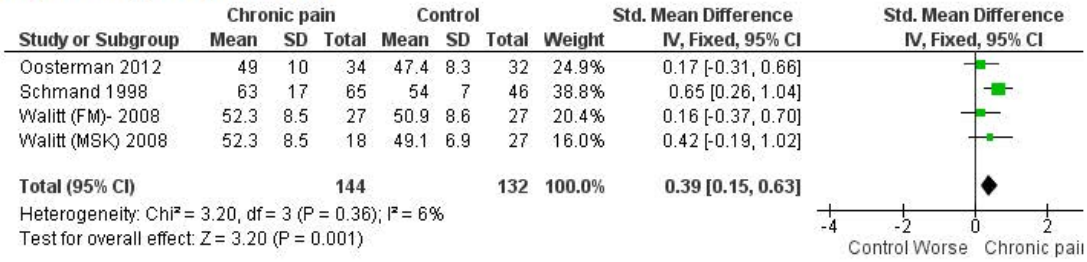
Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.16 TEA-selective attention.

Figure 16 (Analysis 1.17)



Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.17 Stroop Color.

Figure 17 (Analysis 1.18)

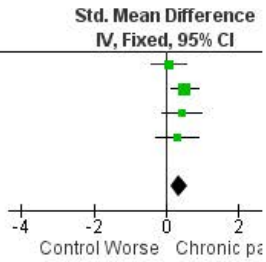


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.18 Stroop-Word.

Figure 18 (Analysis 1.19)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Oosterman 2012	99.4	21.7	34	97.7	24.6	32	24.8%	0.07 [-0.41, 0.56]
Schmand 1998	99	30	65	86	17	46	39.3%	0.51 [0.12, 0.89]
Walitt (FM)- 2008	54.1	9.5	27	50	9.7	27	19.8%	0.42 [-0.12, 0.96]
Walitt (MSK) 2008	52.9	9.3	18	50	9.7	27	16.1%	0.30 [-0.30, 0.90]
Total (95% CI)			**144**			**132**	**100.0%**	**0.35 [0.11, 0.59]**

Heterogeneity: Chi² = 2.01, df = 3 (P = 0.57); I² = 0%
Test for overall effect: Z = 2.84 (P = 0.004)

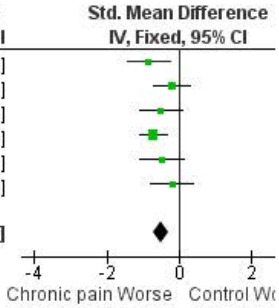


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.19 Stroop Card/ Word.

Figure 19 (Analysis 1.20)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Gimse 1997	11.65	2.46	23	13.35	1.37	26	13.2%	-0.85 [-1.44, -0.27]
Grace 1999	53.57	9.09	30	55.2	6.9	30	17.8%	-0.20 [-0.71, 0.31]
Ho Kim 2012	55.9	9.6	23	60.9	9.6	24	13.5%	-0.51 [-1.09, 0.07]
Schmand 1998	48.6	8.8	65	54.9	8.2	46	30.1%	-0.73 [-1.12, -0.34]
Shur (FM-B) 2003	9.7	2.9	23	11.1	2.7	21	12.7%	-0.49 [-1.09, 0.11]
Shur(PC-R) 2003	10.5	3.2	22	11.1	2.7	21	12.7%	-0.20 [-0.80, 0.40]
Total (95% CI)			**186**			**168**	**100.0%**	**-0.52 [-0.74, -0.31]**

Heterogeneity: Chi² = 5.02, df = 5 (P = 0.41); I² = 0%
Test for overall effect: Z = 4.81 (P < 0.00001)

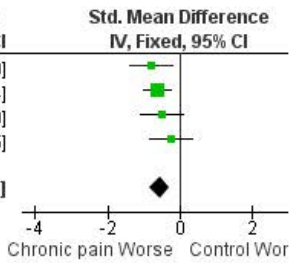


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.20 RAVLT-immediate recall.

Figure 20 (Analysis 1.21)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Ho Kim 2012	11.7	2.5	23	13.4	1.6	24	18.7%	-0.80 [-1.40, -0.20]
Schmand 1998	10.6	2.8	65	12.3	2.5	46	44.5%	-0.63 [-1.02, -0.24]
Shur (FM-B) 2003	9.2	2.9	23	10.7	2.9	21	18.4%	-0.51 [-1.11, 0.09]
Shur(PC-R) 2003	9.9	3.3	22	10.7	2.9	21	18.5%	-0.25 [-0.85, 0.35]
Total (95% CI)			**133**			**112**	**100.0%**	**-0.57 [-0.83, -0.31]**

Heterogeneity: Chi² = 1.78, df = 3 (P = 0.62); I² = 0%
Test for overall effect: Z = 4.33 (P < 0.0001)

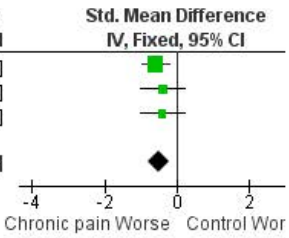


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.21 RAVLT-delayed recall.

Figure 22 (Analysis 1.22)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Schmand 1998	28.4	2.7	65	29.7	0.9	46	54.8%	-0.60 [-0.99, -0.21]
Shur (FM-B) 2003	13.5	1.4	23	14.9	4.8	21	22.9%	-0.40 [-0.99, 0.20]
Shur(PC-R) 2003	13.5	1.4	22	14.9	4.6	21	22.3%	-0.41 [-1.01, 0.20]
Total (95% CI)			**110**			**88**	**100.0%**	**-0.51 [-0.80, -0.23]**

Heterogeneity: Chi² = 0.46, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 3.51 (P = 0.0005)

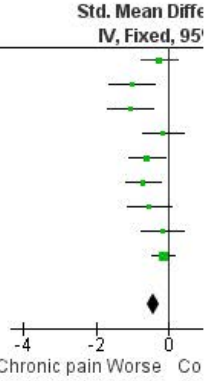


Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.22 RAVLT-delayed recognition.

Figure 23 (Analysis 1.23)

Study or Subgroup	Chronic pain Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Bosma 2002	3	2.2	31	3.7	3.1	30	11.2%	-0.26 [-0.76, 0.25]
DiStefano (24m-G)1995	7.7	4.9	21	14.1	7.2	21	6.8%	-1.02 [-1.67, -0.37]
DiStefano (6m-R) 1995	7.1	4.7	21	14.4	8.4	21	6.7%	-1.05 [-1.70, -0.40]
Gimse 1997	43.09	9.16	23	44.35	7.23	26	9.0%	-0.15 [-0.71, 0.41]
Grace 1999	69.07	22.38	30	82.6	22.22	30	10.6%	-0.60 [-1.12, -0.08]
Leavitt 2007	5.2	2.5	35	7.1	2.8	35	12.2%	-0.71 [-1.19, -0.22]
Shur (FM-B) 2003	37.3	12.7	23	43.7	10.4	21	7.8%	-0.54 [-1.14, 0.06]
Shur(PC-R) 2003	41.6	14.4	22	43.7	10.4	21	7.9%	-0.16 [-0.76, 0.44]
Sjogren 2005	32.3	12.7	91	33.9	8.1	64	27.8%	-0.14 [-0.46, 0.18]
Total (95% CI)			**297**			**269**	**100.0%**	**-0.43 [-0.60, -0.26]**

Heterogeneity: Chi² = 13.73, df = 8 (P = 0.09); I² = 42%
Test for overall effect: Z = 4.97 (P < 0.00001)



Forest plot of comparison: 1 Cognitive impairment in Chronic Pain versus Healthy Control, outcome: 1.23 PASAT.

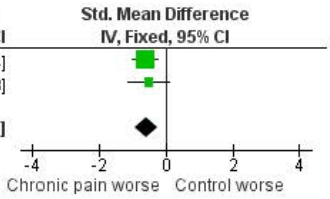
RESTRICTED ANALYSIS

Figures

Figure 1 (Analysis 2.1)

Study or Subgroup	Chronic pain worse Mean	SD	Total	Control worse Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Schmand 1998	57.9	10.3	65	64	8.8	46	71.3%	-0.62 [-1.01, -0.24]
Shur(PC-R) 2003	10.5	2.5	22	11.8	2.3	21	28.7%	-0.53 [-1.14, 0.08]
Total (95% CI)			**87**			**67**	**100.0%**	**-0.60 [-0.92, -0.27]**

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 3.58 (P = 0.0003)

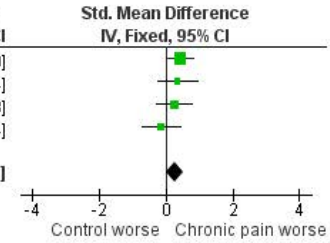


Forest plot of comparison: 2 Restricted analysis chronic pain patients performance on NP test, outcome: 2.1 WAIS- Digit symbol.

Figure 2 (Analysis 2.2)

Study or Subgroup	Chronic pain worse Mean	SD	Total	Control worse Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Schmand 1998	35	13	65	30	10	46	43.1%	0.42 [0.04, 0.80]
Shur(PC-R) 2003	27.7	10.3	22	24.7	6.9	21	17.3%	0.33 [-0.27, 0.94]
Walitt (FM)- 2008	54.6	14.3	27	51.5	10.2	27	21.9%	0.25 [-0.29, 0.78]
Walitt (MSK) 2008	50	8.8	18	51.5	10.2	27	17.6%	-0.15 [-0.75, 0.44]
Total (95% CI)			**132**			**121**	**100.0%**	**0.27 [0.01, 0.52]**

Heterogeneity: Chi² = 2.56, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 2.08 (P = 0.04)

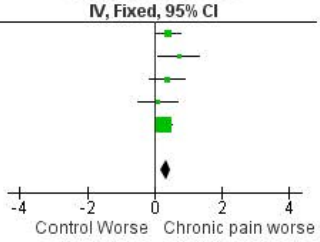


Forest plot of comparison: 2 Restricted analysis chronic pain patients performance on NP test, outcome: 2.2 TMT-A.

Figure 3 (Analysis 2.3)

Study or Subgroup	Chronic pain worse Mean	SD	Total	Control worse Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Schmand 1998	69	23	65	60	22	46	18.8%	0.40 [0.01, 0.78]
Shur(PC-R) 2003	72	36.1	22	52.3	11.2	21	7.1%	0.72 [0.10, 1.34]
Walitt (FM)- 2008	52.1	10.2	27	48.1	11.2	27	9.4%	0.37 [-0.17, 0.91]
Walitt (MSK) 2008	49.1	9.6	18	48.1	11.2	27	7.7%	0.09 [-0.50, 0.69]
Weiner 2006	53.7	11.36	163	50.73	10.22	160	56.9%	0.27 [0.05, 0.49]
Total (95% CI)			**295**			**281**	**100.0%**	**0.32 [0.16, 0.49]**

Heterogeneity: Chi² = 2.48, df = 4 (P = 0.65); I² = 0%
Test for overall effect: Z = 3.83 (P = 0.0001)

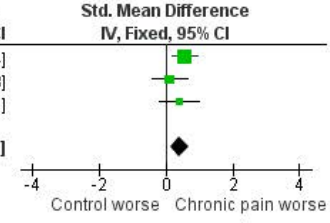


Forest plot of comparison: 2 Restricted analysis chronic pain patients performance on NP test, outcome: 2.3 TMT-B.

Figure 4 (Analysis 2.4)

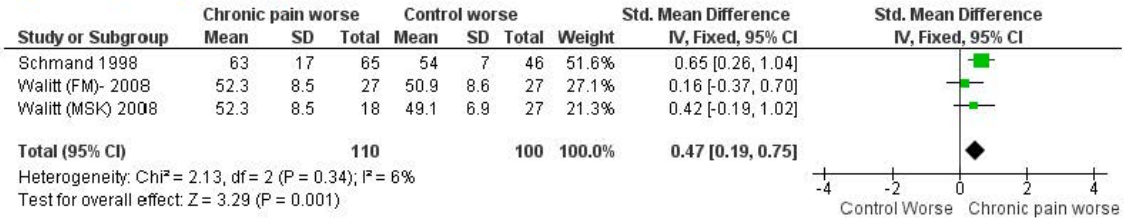
Study or Subgroup	Chronic pain worse Mean	SD	Total	Control worse Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Schmand 1998	47	13	65	41	6	46	51.9%	0.56 [0.17, 0.94]
Walitt (FM)- 2008	50.4	7.2	27	49.7	7.9	27	27.0%	0.09 [-0.44, 0.63]
Walitt (MSK) 2008	50.4	7.2	18	47.4	7.3	27	21.2%	0.41 [-0.20, 1.01]
Total (95% CI)			**110**			**100**	**100.0%**	**0.40 [0.12, 0.68]**

Heterogeneity: Chi² = 1.93, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 2.83 (P = 0.005)



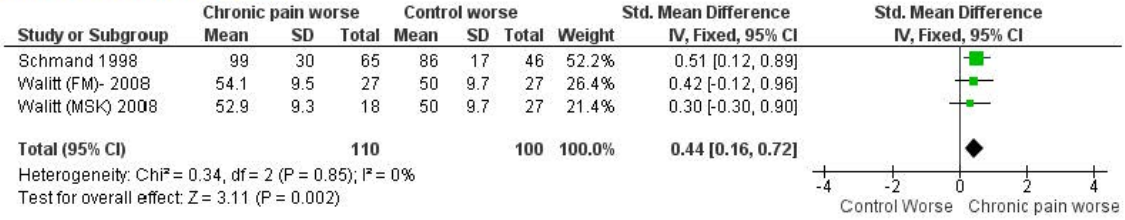
Forest plot of comparison: 2 Restricted analysis chronic pain patients performance on NP test, outcome: 2.4 Stroop Color.

Figure 5 (Analysis 2.5)



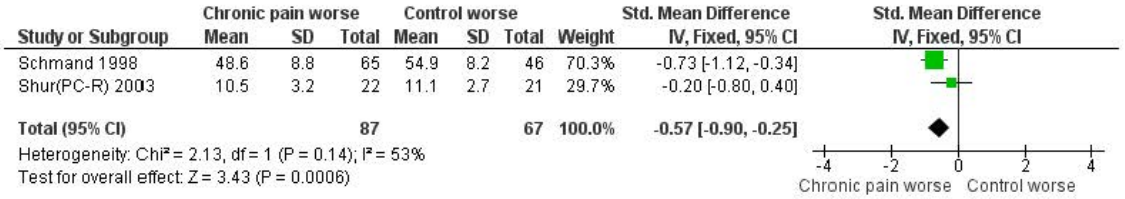
Forest plot of comparison: 2 Restricted analysis chronic pain patients performance on NP test, outcome: 2.5 Stroop Word.

Figure 6 (Analysis 2.6)



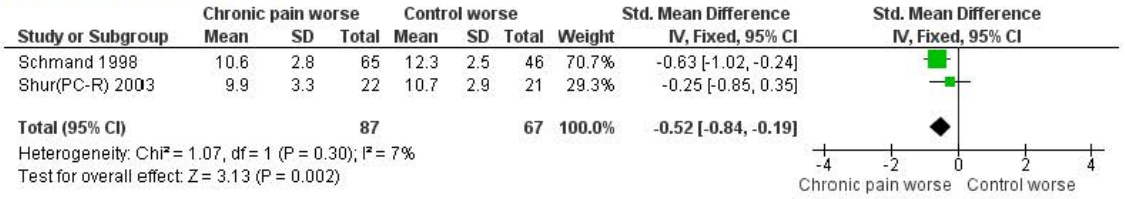
Forest plot of comparison: 2 Restricted analysis chronic pain patients performance on NP test, outcome: 2.6 Stroop Color/ Word.

Figure 7 (Analysis 2.7)



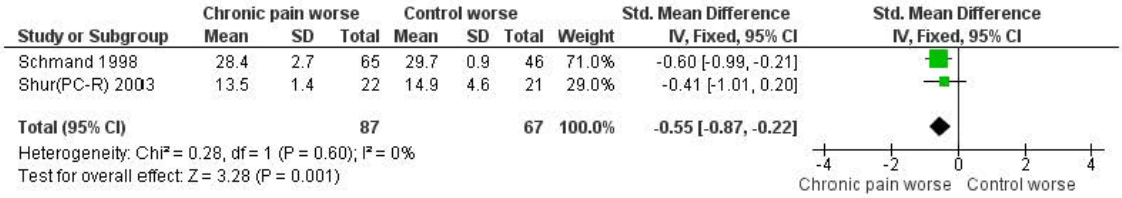
Forest plot of comparison: 2 Restricted analysis chronic pain patients performance on NP test, outcome: 2.7 RAVLT- Immediate recall.

Figure 8 (Analysis 2.8)



Forest plot of comparison: 2 Restricted analysis chronic pain patients performance on NP test, outcome: 2.8 RAVLT- Delayed recall.

Figure 9 (Analysis 2.9)



Forest plot of comparison: 2 Restricted analysis chronic pain patients performance on NP test, outcome: 2.9 RAVLT- Delayed recognition.

TABLES

Table# 1: Comparison of societal burden associated with chronic pain in different countries

Country	**Total participants**	**Male and female**	**Peak age**	**Identified risk factors and burden**
Australia (Blyth et al 2001**)**	17543	17.1% male and 20% females	Males: 31% (80-90) Females: 27% (65-69)	Age, female, low education level, unemployment , disability benefits, psychological distress
15 European countries + Israel (Breivik et al 2006)	19% (4839) of the 46,394	19% adult population,		Depression (21%), work disability (61%), loss of work (19%), change jobs (13%), doctor visit (60%), currently treated 2%
Gore et al 2012 (USA)	101294	55%(F)	47.2 (F)	depression (13.0%) anxiety (8.0%), sleep disorders (10.0%); Pain related pharmacotherapy (*P* <0.0001); opioids (37.0%) NSAIDS (26.2%), Tramadol (8.2%), combination CLBP; 36.3% Health care costs were significantly (*P* <0.0001), Total direct medical costs were estimated at $8386 - 17,507 in the CLBP group and $3607-$10,845 in the control (*P* <0.0001).
Johannes et al 2010 (USA)	27035	34.3(F); M (26.7)	64 (42.5%) 21.8% (M)	Unemployment, low SES
Meana et al 2004 (Canada)	125574	185 (F); 14% (M)	65	Age and socio-economic variables, Psychological distress (Depression prevalence among patients with chronic pain

				(31% to 100%); pain complaints in (depressed (34% to 66%).

Table #2: Gilmour: 2003 Canadian Community Health Survey; Populations 135,573				
Condition	**Gender (%)**	**Age (above 30; %)**	**ADL**	**IADL**
Arthritis	37.7 (M); 54.7 (F)	47.3 (M); 16.6 (F)	8% (M), 9% (F)	20% (M); 35% (F)
Back pain	21.6(M); 26.1(F)	24.1 (M); 22.7 (F)	9% (M); 10% (F)	21% (M); 41% (F)
Migraine	3.6 (M) 6.8 (F)	5.4 (M); 11.9 (F)	10% (M); 12% (F)	28% (M); 37% (F)
Fibromyalgia	1.1(M) 2.6 (F)	1.9 (M); 1.9 (F)	13% (F)	27% (M); 46%(F)

Table #3: Ramage Morin 2005 P; Chronic pain in Canadian seniors; Total number of participants from 1994-2001 : institutionalized (1465 and households (7130)				
Demographics	Household % (27%)		Institution % (38%)	
	Male	Female	Male	Female
18-64 (15.5%)	14	16.9		
65/older (	21.	31.2	33.9	39.4
EDCATION (<12 grade)	29.5		40.7	
Education (>12 grade)	23.3		32.6	
Income (low)	28.1		40.2	
Income (moderate)	25.4		37.2	
Income (higher)	22.8		34.7	
52.7 % of the total 21.8% in household and 63.8% out of the 42.3 % percent reported severe pain that interfered with their routine activities of daily living, satisfaction with pain control and happiness.				

Table # 4: CHRONIC PAIN PREVALENCE (Health Canada; Reitsma 2011)		
Canadian population	**1994-95**	**18.9%**
	1996-97	**15. 1%**
	2007-08	**18.5%**
Gender	**female**	**16.5-21.5%**
Age	**65+**	**23.9-31.3%**
	Woman 65+	**26.0- 34.2%**
Impact on activities		**11.4- 13.3% (patient have to give-up job or routine activities)**

Table# 5: Pain In Canada Fact Sheet; The Canadian Pain society; 2013

- Only 30% of ordered medication is given,
- 50% of patients are left in moderate to severe pain after surgery
- Acute postoperative pain is followed by persistent pain in 10---50% of individuals after common surgical procedures (groin hernia repair, breast and thoracic surgery, knee and hip replacements etc.). This pain is severe in 2---10% of cases.
- 9.2% of patients on waitlists for treatment at Canadian pain clinics identify surgery as the
- Cause of their chronic pain
- More than 50% of people waiting for care at Canadian pain clinics have severe levels of depression and 34.6% report thinking about suicide , 72.9% report the pain interferes with
- Their normal work
- Pain is the most common reason for seeking health care and as a presenting complaint accounts for up to 78% of visits to the emergency department. Recent research continues to document high pain intensity and suboptimal pain management in a large multicenter emergency department network in Canada
- One in five Canadian adults suffer from chronic pain
- Children are not spared. One in five Canadian children have Weekly or more frequent chronic pains (most commonly headaches, stomachaches, and muscle/joint/back pain), with estimated 5---8% of children or teenagers suffering from chronic pain severe enough that it
- Interferes with schoolwork, social development and physical activity
- The prevalence of chronic pain increases with age with the prevalence of chronic pain as high as
- 65% .In community dwelling seniors and 80% Of older adults living in long term care facilities and this pain is under recognized and undertreated
- Chronic pain is associated with the worst quality of life as compared with other chronic diseases such as chronic lung or heart disease
- US figures have documented that the cost of chronic pain in adults including health care expenses and lost productivity is $560---$630 Billion annually. Based on these figures it is estimated that the annual cost of chronic pain in Canada is at least $56---60 Billion dollars
- People living with pain have double the risk of suicide as compared with people without chronic pain
- A recent review of opioids (narcotic) related deaths in Ontario, identified the tragic fact that pain medication related deaths in Ontario are increasing and that most of the people who died had been seen by a physician within 9-11 days prior to death (emergency room visits and office visits respectively) and the final encounter with the physician involved a mental health or pain related diagnosis. In almost a quarter of the cases the coroner had determined that the manner of death was suicide
- Veterinarians receive 5 times more training in pain management than people

doctors

- Pain research is grossly under---funded in Canada with less than 1% of total funding from Canadian Institutes of Health Research and only 0.25% of total funding for health research going to pain related studies

Table # 6: Schopflocher 2011: Prevalence of chronic pain, Canada 2007 to 2008, according to region (18 years of age or older)

Region	**Chronic pain prevalence**
Atlantic	21.9 %
Quebec	15.7
Ontario	16.6
Prairie	19.6
Alberta	20.6
British Columbia	21.8
Overall in Canada	18.9

Table# 7: Philips 2006; Prevalence, Direct Cost and productivity cost in different countries		
Germany	Low back pain	10 Billion (US$ 5 Billion/ year
Netherland	RA	DFL 11,550 per patient (US$ 5600 in the first six years
England	66 million over the counter purchases for pain medications	GBP 510 Million/ USD 940 million
England	34 million prescriptions Non opioids prescription	GB£120 million [US$220 million])
	NSAIDs18 million prescriptions	GB£150 million or US$280 million
Europe		27% of respondents ever sought medical and at least 38% of this group had constant or daily pain
UK	Primary care cost	4.6 million appointments per year (equivalent to 793 full-time general practitioners, at a total cost of approximately GB£69 million (US$128 million)
	Home tutoring	GB£4400 or (US$8100) on average, per adolescent, per year
	Pain management group	GB£7900 (US$14,600),
USA	lost productive work time	US$7.11 billion
UK		3000 people go on to the incapacity benefit but 300 ever return to work
Germany	Productivity loss	E24.5 million (US$30.8 million)
USA	presenteeism	US$61 billion/year
Australia	Days off from work	Aus$5.1 (US$3.8billion)

Tables #8: Literature search strategy (Animal model only; 1946-2013)		
S#	**Search**	**Result**
1	Chronic pain.mp. or Chronic Pain	22320
2	Cognition/ or cognition	129151
3	Attention.	285050
4	Learning/ or learning	236556
5	Decision making	127872
6	Memory	183656
7	Aversive learning	272
8	Mental flexibility	347
9	Executive function	9995
10	Rodent gambling task	8
11	Operant nose-poke task	1
12	Novel object recognition	761
1	Acquisition and probe	1800
14	Chronic Pain/	111530
15	Inflammatory pain	2637
16	Neuropathic pain	15627
17	1 or 14 or 15 or 16	133471
18	2 or 3 or 4 or 5 or 6 or 7 or 8 or 9	805433
19	Neuropsychological Tests	69192
20	10 or 11 or 12 or 13 or 19	71705
21	17 and 18 and 20	252
22	limit 21 to (English language and animals)	21

Table# 9: Summary of the animal model studies				
Reference	**Animal model**	**Cognitive domain**	**Cognitive test**	**result**
Boyette-davis et al 2008	Rat	Attention	Operant nose-poke tas	Increased number of omissions in pain model
Caine et al 1997	Rat	Spatial learning, recognition memory and attention	Operant delayed non-matching to position lever press task	Decrease in accuracy and decrease in number of rewards earned in pain model
Hu et al 2010	Rat	Spatial learning and memory	acquisition and probe)	Increased latency to platform during acquisition and decreased frequency in platform zone during probe in pain model
Ji et al 2010	Rat	Emotional decision making	Rodent gambling task	Increased preference for high risk level associated with larger, more infrequent rewards in pain model
Kodama et al 2011	Mice	recognition memory	novel-object recognition	impaired recognition ability
Leite-Almedia et al 2009	Rat	Spatial learning and memory and cognitive flexibility	(traditional acquisition and reversal)	Decreased % of distance swam in new platform location and increased % in old location in pain model
Linder et al 1999	Rat	Spatial learning, recognition memory and attention	Operant delayed non-matching to position lever press task	Decrease in accuracy and decrease in response latency
Millecamps et al 2004	Rat	Recognition memory, attention	Novel object recognition	Decrease in attention towards novel object in pain model
Pais Vieira et al 2012	Rat	risk preference,	Rodent gambling	orbitofrontal cortex encoding of risk

		decision	task	preference is compromised in chronic pain animals
Pais Vieria et al 2009-b	Rat	Emotional decision making	Rodent gambling task	Increased preference for high risk level associated with larger, more infrequent rewards and increase in number of omissions in pain model
Pais-Vieira et al 2009- a	Rat	Attention	Operant nose-poke task	Decrease in accuracy, increased number of omissions and increase in preservative responses in pain model
Suzuki et al 2007	Mouse	Aversive learning	Passive avoidance	No impairment of passive avoidance response in pain model

Table# 10: Cortical structure involved in pain and cognition processing	
Frontal cortex (Pre frontal and DLPFC)	Working memory, executive functions, inhibition, emotions, behaviour
SMA, Pre SMA	Inhibition and pain response , motor action
Insula	Pain processing, pain affect, emotional signals, error detection, competing response, attention
Cingulate gyrus	Motivation, affect, role in “Priming”, emotional signals, error detection, competing response, attention
Inferior temporal gyrus, fusiform gyrus	Object recognition
Inferior parietal cortex	Information processing, switching attention, phonology, Working memory and pain threshold

Table# 11:Shows different cortical area involvement in Chronic pain (Tables made from Smallwood 2013 results)		
Brain region	**cluster**	**Role/ function**
Inferior Frontal gyrus	1, 7, 12	Pain catastrophizing, language processing and working Memory, and contributes to emotional empathy increased in CP and related with pain intensity, emotional states,
Anterior Insula	1, 3, 5, 12	Pain processing, affective pain processing,
Putamen	1	Somatotopic pain processing, modulates superior temporal gyrus. Emotional processing, cognition, pain perception, cognitive language, modulates STG activity
Anterior cingulate gyrus	2	Experimental pain, chronic pain, affective pain processing, pain avoidance, fear Emotion, cognition, pain perception,
Superior temporal gyrus (STG)	3, 5	Auditor perception, speech perception and comprehension, Inhibition, speech, audition, language and music, efference copy mediated by putamen
Thalamus	4	Affective and sensory process, speech execution,
Posterior Cingulate	6, 8 (SMA)	Skeletal motor orientation, Somatotopy sensations, execution of motor learning, learning, explicit memory and action
Superior frontal gyrus	9	Working memory, spatial process, pain processing, coping styles
Middle frontal gyrus	10, 11	Working memory, cognition, pain intensity (pre-motor cortex), extends in to SFG

Table# 12: Changes in cortical regions on MRI and perfusion studies		
Luerding 2008		
NP test	**Brain part involved**	**Correlation**
Non verbal WM (Corsi Block)	Middle frontal gyrus	Positive
Verbal memory (Digit span BW)	Medial frontal lobe Superior frontal cortex SMA	Positive
Pain score (SES)	Frontal gyrus	Negative
Co-joint SES/Digit span BW	Medial frontal lobe ACC	
White matter changes		
Digit span BW	m-cingulate gyrus, ACC	Positive
SES	Mid cingulum , ACC, Peri genual white matter	Negative
Changes in perfusion (Glass 2011)		
No Go > Go	mid-cingulate cortex (MCC)/SMA Right premotor/ pre-central cortex (middle frontal gyrus, BA 6/9), Right inferior parietal lobule, Left dorsolateral prefrontal cortex (middle frontal gyrus, BA 9) Left lentiform nucleus.	Decreased activation
	Right inferior temporal gyrus/fusiform gyrus	Increased activation
Anxiety scores	Inhibition (SFG, inferior TG, fusiform gyrus)	Negatively
	Right IC, right IFG, right ACC, right superior frontal gyrus, and putamen bilaterally, and left middle/superior temporal gyrus.	Correlated positively with BOLD
Mental fatigue	Left ICand putamen	Correlated positively with BOLD
	Right inferior temporal gyrus/fusiform gyrus, the right orbitofrontal cortex and the left cerebellum	Negative correlation
Functional connectivity	Right inferior temporal gyrus/fusiform gyrus Between Acc and medial frontal gyrus Projecting to the pre-SMA, during inhibition	Increased connectivity

Table# 13: pain population in this meta-analysis			
Pain type	**Total participants**	**Percentage**	**Studied**
WL	170	14.24%	5
FM	593	49.70%	13
MSK	228	19.11%	4
RA	20	1.67%	1
NO SPECIFIED	182	15.25%	4
TOTAL	**1193**		

Table# 14: Administration of neuropsychological test in this meta-analysis	
TEST NAME	**DESCRIPTION OF THE TEST**
ROCF	The scoring criteria used is based upon Osterreith's original test procedure which defined 18 units of the drawing, assigning point values of 0–2 to each unit dependent upon the degree to which the units are correctly drawn and placed. Each element of the ROCF test had a maximum score of 36.
PASAT	Sixty numbers, all less than 10,are read from a tape every others. Each time a number is read, it is to be added to the last number read: For a recited list of the numbers 4-6-3-8-2, the answers should therefore be 10-9-1 1-10. The test consists of five trials containing 60 digits each. The intervals between consecutive digits for the five trials were 2.4, 2.0, 1.6, 1.2 and 0.8 s, respectively. The level of performance was expressed by the average error score of the completed trials.
TMT- A	Encircled numbers from I to 25 are randomly written and spaced on a sheet of paper. The task is to draw a line from 1 to 2 to 3, and so forth all the way to 25, working as quickly as possible. The test administrator points out any mistakes and these must be corrected. The total time for completion of the task is recorded (Part A).
TMT-B	Then another sheet of paper is presented to the subject. On this sheet, the letters A through L are intermingled with the numbers 1-25. The task is to draw a continuous line which alternates between the digit series and the alphabet series: l-A-2-B-3-C-4-D, and so forth. The score is the time necessary for completion of the task (Part B).
Stroop test	This test consists of three cards, namely the Word (W) card, the Colour (C) card, and Colour/Word (C/W) card. The W card consists of 10 rows with 10 colour names in each row which all is printed in black ink. The participant is required to read aloud these color names as fast as possible. For the C card, 10 rows are presented containing 10 colored blocks per row, which the participant is required to name as fast as possible. On the C/W card, colour names are printed in an incongruent color, and the participant is required to name the colors in which the words are printed as fast as possible. The time needed to finish each of the cards was measured.
Digit span forward	The Digit Span Forward task involves repeating forward orally presented sequences of single numerals. It was originally included in conventional intelligence tests [28]. The test proceeds by adding one more number to the sequence until two failures are made at a given span length. The task is conceptualized as a measure of immediate auditory (short-term) memory span.
Digit span backward	This task series of digits of increasing length (2 to 9) are orally presented. After each presentation, participants are requested to repeat

	the digits reversing the order in which they were presented.
Corsi block backward	It involves mimicking as subject taps a sequence of up to nine identical spatially separated blocks. The sequence starts out simple, usually using two blocks, but becomes more complex until the subject's performance suffers.
TEA	This test has following components: Map search - Subjects have to search for symbols on a colored map. The score is the number out of 80 found in 2 minutes. Elevator counting - Subjects are asked to pretend they are in an elevator whose door-indicator is not functioning. They therefore have to establish which 'door' they have arrived at by counting a series of tape-presented tones. Elevator counting with distraction - Subjects has to count the low tones in the pretend elevator while ignoring the high tones. This was designed as a subtest of auditory selective attention. Visual elevator - Here, subjects have to count up and down as they follow a series of visually presented 'doors' in the elevator. Auditory elevator with reversal - The same as the visual elevator subtest except that it is presented at fixed speed on tape. Telephone search - Subjects must look for key symbols while searching entries in a simulated classified telephone directory. Telephone search dual task - Subject must again search in the directory while simultaneously counting strings of tones presented by a tape recorder.
RAVLT	From an audiocassette, 15 words are read out loud at I-s intervals (List A). List A is read a total of five times, and after each presentation the subject repeats the words he/ she remember. After the fifth presentation, the number of words the person remembers is recorded (Rey *5).* Subsequently, to distract the subject's learning process, another list (List B) is read, and the subject repeats as many words as possible from this list. Immediately following this exercise the subject is asked to repeat any words remembered from the first list, List A (Rey 6). After engaging in other activity for a half hour, the subject is again asked to repeat as many words as possible from List A (Rey 7). The memory loss resulting from intervention is noted as Rey 5-6, and the loss of memory in time is noted as Rey 5-7.
WCST	In this task, participants are required to sort cards according to the several different dimensions (i.e., color, form, and number); the sorting principle must be deduced from verbal feedback provided by the computer. Once a particular response mode is established (i.e., 10 consecutive correct responses), a new sorting principle (concept) is instituted without warning and must be deduced by the participant. Measures of performance included the number of categories completed, and total and perseverative errors.
SDMT	The task is to write digits under nine arbitrary symbols as quickly as possible during 90 seconds. At the top of the test sheet is a printed key

	that pairs each symbol with a digit.

Table# 15: REPORTING OF COGNITIVE TEST AND DOMAIN MEASURED			
Author	**Cog Domain measured**	**Report result**	**Reporting of result**
Corsi Block spatial forward			
Cánovas 2009	Visuospatial memory	P <0.05	# of correct blocks
Ho Kim 2012	Visuospatial memory Working memory	P <0.05	# of correct blocks
Di Stefano 1995	Visuospatial memory	P <0.05	# of correct blocks
PASAT (Paced Auditory Serial Addition Test)			
Bosma 2002	Divided attention Sustained attention	NS	# of correct answers
DiStefano 1995	Divided attention	P <0.05	error scores reported
Gimse 1997	Divided attention	P <0.05	# of correct answers
Grace 1999	Sustained attention sensitive to information processing	P <0.05	# of correct responses
Leavitt 2006	Sustained attention Divided attention	P <0.05	# of correct answers
Suhr 2003	Attention Working memory	NS	# of correct answers
Sjogren 2005	Information processing speed Working memory; Attention	NS	# of correct answers
RAVLT- Immediate recall			
Gimse 1997	Learning and recall	P <0.05	# of words recalled
Grace 1999	Learning	P <0.05	# of words recalled
Ho Kim 2012	Verbal learning performance	P <0.05	# of words recalled
Schmand 1998	Verbal learning	P <0.05	# of words recalled
Suhr 2003	Visual and verbal memory	NS	# of words recalled
RAVLT delayed recall			
Gimse 1997	Learning and recall	P <0.05	# of words recalled
Ho Kim 2012	Verbal learning performance (verbal memory)	P <0.05	# of words recalled
Schmand 1998	Verbal learning	P <0.05	# of words recalled
Suhr 2003	Learning Visual and verbal memory	NS	# of words recalled

Table# 15: REPORTING OF COGNITIVE TEST AND DOMAIN MEASURED			
Author	**Cog Domain measured**	**Report result**	**Reporting of result**
RAVLT- delayed recognition			
Schmand 1998	Verbal learning	P <0.05	# of words recognized
Suhr 2003	Visual and verbal memory	NS	# of words recognized
Stroop-C			
Oosterman 2012	Inhibition (Executive function and attention)	NS	time needed to complete
Schmand 1998	Perceptual interference Inhibition Selective attention	P <0.05; time to complete	time needed to complete
Walitt 2008	Selective attention Cognitive flexibility	P <0.05	time needed to complete
Stroop-W			
Oosterman 2012	Inhibition	NS	time needed to complete
Schmand 1998	Perceptual interference Inhibition Selective attention	P <0.05	time needed to complete
Walitt 2008	Selective attention Cognitive flexibility	P <0.05	time needed to complete
Stroop-C-W			
Bosma 2002	Selective attention Interference susceptibility	P <0.05	time needed to complete
Oosterman 2012	Inhibition	NS	time needed to complete
Schmand 1998	Perceptual interference Inhibition Selective attention	P <0.05	time needed to complete
Walitt 2008	selective attention cognitive flexibility	P <0.05	time needed to complete
TEA- Selective attention			
Dick 2002	Selective attention	P <0.05	Sum of correct responses
Dick 2008	Selective attention	P <0.05	Sum of correct responses
TEA- Sustained attention			
Dick 2002	Sustained attention	(R, G)=NS	Sum of correct responses
Dick 2008	Sustained attention	P <0.05	Sum of correct responses
TEA- switching attention			
Dick 2002	Switching attention	NS	Sum of correct responses
Dick 2008	Switching attention	NS	Sum of correct responses
TEA- Working memory			
Dick 2002	Working memory	(G)= NS	Sum of correct responses

Table# 15: REPORTING OF COGNITIVE TEST AND DOMAIN MEASURED			
Author	**Cog Domain measured**	**Report result**	**Reporting of result**
Dick 2008	Working memory	P<0.05	Sum of correct responses
TMT-A			
Bosma 2002	Visual scanning	NS, percentile scores	time in seconds to complete
DiStefano 1995	Information processing speed	P <0.05	time in seconds to complete
Gimse 1997	Mental speed	P <0.05	time in seconds to complete
Oosterman 2012	visual speed and mental scanning speed)	P <0.05	time in seconds to complete
Schmand 1998	Visual scanning, Visuomotor tracking	P <0.05	time in seconds to complete
Suhr 2003	Complex psychomotor speed	NS	time in seconds to complete
Walitt 2008	Visual search, sequencing, mental flexibility, and motor speed	P <0.05	time in seconds to complete
TMT-B			
Bosma 2002	Cognitive flexibility	NS	time in seconds to complete
DiStefano 1995	Information processing speed	P <0.05,	time in seconds to complete
Gimse 1997	Mental speed	P <0.05	time in seconds to complete
Oosterman 2012	Mental flexibility	NS	time in seconds to complete
Schmand 1998	Mental flexibility	P <0.05	time in seconds to complete
Suhr 2003	Complex psychomotor speed	NS	time in seconds to complete
Walitt 2008	Visual search, sequencing, mental flexibility, and motor speed	P <0.05	time in seconds to complete
Weiner 2006	Mental flexibility	P <0.05	time in seconds to complete
WAIS Digit span (forward/ backward)			
Di Stefano 1995	Attention	P <0.05	# of correct digits/ answers
Leavitt 2006	Attention& concentration	P <0.05	Sum of correct digits/ answers
Suhr 2003	Attention Working memory	NS	# of correct digits/ answers
WAIS Digit span forward			
Cánovas 2009	Visuo-spatial memory,	P <0.05	# of correct digits/ answers

Table# 15: REPORTING OF COGNITIVE TEST AND DOMAIN MEASURED			
Author	**Cog Domain measured**	**Report result**	**Reporting of result**
Ho Kim 2012	Immediate short term memory	P <0.05	# of correct digits/ answers
Landro 1997	Working memory	P <0.05	# of correct digits/ answers
WAIS Digit span backward			
Cánovas 2009	Attention/ working memory	P <0.05	# of correct digits/ answers
Ho Kim 2012	Working memory (short term memory; Verbal Performance intelligence)	P <0.05	# of correct digits/ answers
Landro 1997	Working memory (Short term memory)	NS	# of correct digits/ answers
Oosterman 2011	Working memory	P <0.05	# of correct digits/ answers
WAIS Digit symbol			
Lee 2003	Psychomotor speed Visual scanning	P <0.05	# of correct digits/ answers
Schmand 1995	Visual scanning Manual speed Visuomotor coordination Sustained attention	P< 0.05	# of correct digits/ answers
Suhr 2003	Working memory; Attention	NS	Sum of correct digits/ answers
WCST- No of categories			
Verdejo-Garcia et al 2009	Working memory Distractibility Executive function	P <0.05	# of cards sorted of correctly in category
Suhr 2003	Executive function	NS	# of cards sorted of correctly in category
WCST- % Preservative errors			
Suhr 2003	Executive function	NS	# of cards sorted of correctly in category
Verdejo-Garcia et al 2009	Working memory Distractibility Executive function	P <0.05	# of cards sorted of correctly in category
ROCF- Delayed Recall			
Bosma 2002	Delayed recall	P <0.05	# of figures recalled/ copy
Ho Kim 2012	non-verbal memory (delayed)	P <0.05	# of figures recalled/ copy
Lee 2010	Visual memory	P <0.05	# of figures recalled/ copy
Suhr 2003	Visual and verbal memory	NS	# of figures recalled/ copy

Table# 15: REPORTING OF COGNITIVE TEST AND DOMAIN MEASURED			
Author	**Cog Domain measured**	**Report result**	**Reporting of result**
ROCF Immediate recall			
Bosma 2002	Immediate recall	P <0.05	# of figures recalled/ copy
Ho Kim 2012	non-verbal memory (immediate)	P <0.05	# of figures recalled/ copy
Lee 2010	Visuospatial constructional ability	P <0.05; sum of four tests	# of figures recalled/ copy

Table # 16: DATA & ANALYSIS TABLE- SUMMARY							
Cognitive test	**Cognitive domain**	**Dominant pain type**	**Studies**	**n**	**Effect size**	**CI**	**P-value**
Corsi Block-spatial forward	Visuospatial memory	Whiplash	4	161	-0.26	-0.57, 0.05	0.10
ROCF-Immediate	non-verbal memory Visual memory	Fibromyalgia	3	1647	-0.11	-0.24, 0.01	0.08 I^2= 90%
ROCF-delayed	non-verbal memory Visual memory	Fibromyalgia	5	1734	-0.15	-0.27, 0.03	0.02 I^2= 67
WCST-Perservative errors	Executive function Working memory Distractibility	Fibromyalgia	3	159	0.15	-0.16, 0.47	0.33
WCST- No of categories	Executive function Working memory Distractibility	Fibromyalgia	3	159	-0.29	-0.60, 0.03	0.07 I^2= 63
WAIS digit symbol	Working memory, Attention	Fibromyalgia	5	1797	-0.34	-0.45, -0.22	0.00001
WAIS-digit span forward	Working memory	Fibromyalgia	3	120	-0.19	-0.53, 0.19	0.36
WAIS-digit span backward	Working memory	Fibromyalgia	4	186	-0.39	-0.68, -0.10	0.009
WAIS-digit span	Working memory	Fibromyalgia	5	241557	-0.20	-0.45	0.12

	Attention					, 0.05	
TMT-A	psychomotor speed Visual scanning	Whiplash	10	557	0.32	0.15 , 0.49	0.0002
TMT-B	Mental flexibility psychomotor speed	Fibromyalgia	10	180	0.38	0.25 , 0.52	0.00001
TEA-Working memory	Working memory	Fibromyalgia	4	180	-0.92	-1.24 , -0.61	0.00001
TEA-Switching	Switching attention	Fibromyalgia	3	120	-0.44	-0.80 , -0.07	0.02
TEA-Sustained attention	Sustained attention	Fibromyalgia	4	180	-0.77	-1.07 , -0.46	0.00001
TEA-Selective attention	Selective attention	Fibromyalgia	4	180	-0.87	-1.18 , -0.56	0.00001
Stroop color	Perceptual interference Inhibition Selective attention	Fibromyalgia	4	276	0.37	0.13 , 0.61	0.003
Stroop word	Perceptual interference Inhibition Selective attention	Fibromyalgia	4	276	0.31	0.07 , 0.55	0.01
Stroop C/W	Perceptual interference Inhibition Selective attention	Fibromyalgia	4	276	0.35	0.11 , 0.59	0.004

RAVLT-immediate recall	Verbal learning and memory	Fibromyalgia	6	354	-0.52	-0.74, -0.31	0.00001
RAVLT-delayed recall	Verbal learning and memory	Whiplash	4	245	-0.57	-0.83, -0.31	0.0001
RAVLT delayed recognition	Verbal learning and memory	Whiplash	3	198	-0.51	-0.80, -0.23	0.0005
PASAT	Sustained attention Divided attention	Whiplash	9	566	-0.43	-0.60, -0.26	0.00001

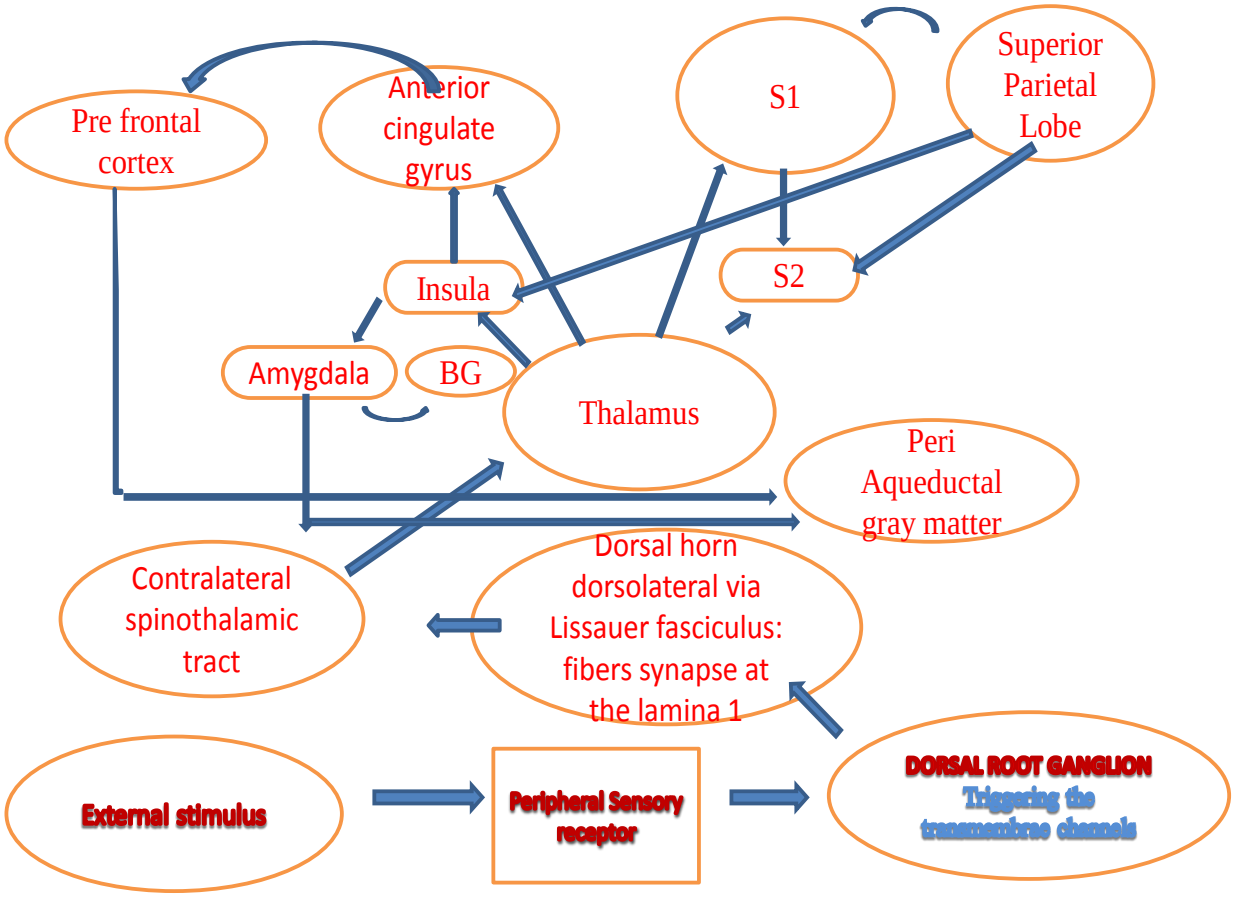
Table # 17: Summary of each cognitive domain and Test in this Meta-Analysis		
Cognitive domain	**Tests**	**results**
Visuospatial memory/ Non verbal/ visual memory	Corsi Block- spatial forward	*No significant*
	ROCF- immediate recall	*No significant*
	ROCF-delayed recall	*No significant*
Executive function, distractibility	WCST Perservative errors	*No significant*
	WCST- % errors	*No significant*
	Stroop test (C W, C/W)	Significant effects was found (Pain type is different)
Working memory	WAIS- digit symbol	Significant effect
	WAIS- digit span forward	*No significant*
	WAIS digit span backward	Significant
	WAIS- digit span	Significant
	TEA- working memory	Significant
Psychomotor speed/ visual scanning	TMT-A	Significant
	Digits symbol	Significant
Mental flexibility	TMT-B	Significant
Switching attention	TEA- switching attention	Significant
Sustained attention/ divided attention	TEA- sustained attention	Significant
	PASAT	Significant
Selective attention	TEA- selective attention	Significant
	Stroop –C	Significant
	Stroop –W	Significant
	Stroop- C/W	Significant
Inhibition, perceptual interference	Stroop –C	Significant
	Stroop –W	Significant
	Stroop- C/W	Significant
Verbal memory	RAVLT- Immediate memory	Significant
	RAVLT- delayed recall	Significant
	RAVLT- delayed recognition	Significant

Table # 18: Comparison of the IQ Uncontrolled and IQ controlled Effect sizes						
Cognitive test	**Analysis # 1**			**Analysis # 2**		
	P value	I^2 (%)	**Effect size**	P value	I^2 (%)	**Effect size**
WAIS Digit symbol	0.00001	8	**-0.34**	0.0003	0	***-0.60***
TMT-A	0.0002	0	**0.32**	0.04	0	***0.27***
TMT-B	0.00001	0	**0.38**	0.0001	0	***0.32***
RAVLT- immediate recall	0.00001	0	**-0.52**	0.0006	53	**-0.57**
RAVLT- delayed recall	0.00001	0	**-0.57**	0.002	7	**-0.52**
RAVLT delayed recognition	0.0005	0	**-0.51**	0.001	0	**-0.55**
Stroop Color	0.0003	0	**0.37**	0.005	0	**0.40**
Stroop Word	0.001	6	**0.39**	0.001	6	**0.47**
Stroop Color/ Word	0.004	0	**0.35**	0.002	0	***0.44***
Minus sign means that chronic pain group performed poorer.						

Figures

Figure 1:

A-Beta (myelinated large fibers): touch, pressure and vibrations
A- Delta (myelinated small fibers): slow; pricking pain, mechanical heat
C-fibers (smallest; slowest): open endings, slow onset and poorly localized pain with burning quality, delayed fashion



ABBREVIATIONS

Abbreviations	Descriptions
ACC	Anterior Cingulate Cortex
BAI	Beck anxiety inventory
BDI	Beck depressive inventory
BOLD	Blood-oxygen-level dependent
CAMK II	Calmodulin-dependent Protein Kinase II
CCHS	Canadian Community Health Survey
CCI	Chronic Constrictive Injury
CLBP	Chronic low back pain
CPSP	Chronic Post Surgical Pain
CSF	Cerebrospinal fluid
CVLT	California Verbal Learning Test
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
FG	Fusiform gyrus
FM	Fibromyalgia
GABA	Gamma Amino Butyric Acid
I^2	Heterogeneity of variance
IASP	International Association for the Study of Pain
IC	Insular cortex
IFC	Inferior Pre-frontal cortex
IGT	Iowa Gambling Task
IPC	Inferior Parietal Cortex
ITG	Inferior Temporal Gyrus
KCFT	Korean version of ROCF
LTP	Long Term Potentiation
MMSE	Mini Mental Test
MoCA	Montreal Cognitive Test
m-PFC	Mid Prefrontal Cortex
MSIT	Multi Source Interference Task
NC-O	NewCastle Ottawa
NE	Nor Epinephrine
NMDA	N-Methyl-D-aspartate
NPHS	National Population Health Survey
NSAIDS	Non steroidal anti-inflammatory drugs
OFC	Orbito Frontal Cortex
OTC	Over the counter
PAG	Peri aqueductal gray matter
PASAT	Paced auditory serial addition test

PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex
PLP	Phantom limb Pain
RA	Rheumatoid Arthritis
RAVLT	Rye Adult Verbal Learning Test
ROCF	Rye Ostrich Complex Figure
RPCQ	Rivermead Post Concussion Questionnaire
SCWT	Stroop Color Word Test
SD	Standard Deviation
SMA	Supplementary Motor Area
SNI	Spinal nerve injury
SNL	Spinal nerve ligation
TEA	Test of everyday attention
TMT	Trail Making Test
TNF	Tissue Necrosis Factor
VLPFC	Ventero-lateral Prefrontal Cortex
VMW	Verbal working memory
VSWM	Visuospatial Working Memory
WAD	Whiplash Associated Disorder
WAIS	Wechsler adult intelligence scale
WCST	Wisconsin card sorting test