



CATÓLICA
INSTITUTO DE CIÊNCIAS DA SAÚDE

LISBOA · PORTO

**A RELAÇÃO ENTRE AS VARIÁVEIS DEMOGRÁFICAS E OS
RESULTADOS ENCONTRADOS NA APLICAÇÃO DO FAST**

INDIVIDUAL DIFFERENCES IN EXPERIMENTAL PAIN VARIABILITY IN
RESPONSE TO THE FOCUSED ANALGESIA SELECTION TEST

Dissertação apresentada à Universidade Católica Portuguesa para obtenção do grau de
mestre em Neuropsicologia

Por

Gisela Pena Antunes

Lisboa, 2021



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Sob a orientação de Professora Doutora Rita Canaipa e
Professor Doutor Roi Treister

Lisboa, 2021

“O sofrimento proporciona a melhor proteção para a sobrevivência, uma vez que aumenta a probabilidade de darmos atenção aos sinais de dor e agirmos no sentido de evitar sua origem ou corrigir suas consequências.”

António Damásio

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Não há palavras para descrever a montanha russa de emoções que foi escrever esta dissertação, mas foi sem dúvida a maior prova de superação e perseverança que já passei na minha vida. A Neuropsicologia foi uma área que ganhou forma na minha vida ao longo dos anos, cada vez mais fico impressionada com as capacidades do ser humano e muito disso deve-se a vários professores, oradores e autores que com as suas descobertas e explicações fazem-me fascinar pela área e, por esse motivo, um obrigado a todos, sem eles não estaria a seguir este percurso.

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Resumo

Introdução: A dor está presente em várias doenças e tem um impacto significativamente negativo na qualidade de vida do sujeito. As dificuldades em definir o conceito, relatar com precisão e avaliar a dor têm sido consideradas os principais motivos do fracasso dos ensaios clínicos em avaliar a eficácia de novos analgésicos. Neste estudo é explicado o conceito e a história da dor, a neuro modulação e as vias ascendentes e descendentes, os diferentes tipos de classificação da dor, o impacto da memória no processamento da dor, as medidas mais comuns utilizadas na avaliação da dor, a forma como as pessoas percebem de forma diferente a dor e os impactos que as variáveis individuais têm no relato das habilidades de dor.

Objetivos: Este estudo baseia-se nos seguintes objetivos: comparar as diferenças na variabilidade experimental do FAST (medido através do R^2 , ICC, CoV) nos dois grupos culturais (Portugal e Israel; estudar a relação entre as diferenças individuais (medidas através de questionários) e as diferenças na variabilidade obtida através do FAST (medido através do R^2 , ICC, CoV); estudar a relação entre as diferenças demográficas (idade, sexo, anos de escolaridade, estado civil e IMC) e as diferenças na variabilidade obtida através do FAST (medido através do R^2 , ICC, CoV); e, por último, correlacionar as relações entre a capacidade de memória a curto prazo (medida através da tarefa Memória de Dígitos) e a variabilidade experimental dos relatos de dor do FAST (medido através do R^2 , ICC, Cov).

Método: Este estudo retrospectivo envolveu a análise dos resultados de 452 indivíduos saudáveis a quem foi aplicado, em dois laboratórios, o teste de seleção de analgesia focada (FAST) que permite medir a variabilidade nos relatos de dor induzida por estímulos experimentais. Foi obtida informação demográfica (idade, género, escolaridade, estado civil e IMC) e de características individuais, através dos seguintes questionários: SCS-R; PSQ; PCS; LOT; BAQ; HADS; MAIA. E, ainda, foi avaliada a memória de curto-prazo, através do teste de Memória de Dígitos.

Resultados: Os dados recolhidos mostraram que há elevada dispersão nos resultados da variabilidade nos relatos de dor. Há associações entre o género, o estado civil e a catastrofização da dor comparativamente com os resultados no FAST e também foram encontradas algumas correlações entre Digit Span e os dois locais do estudo e com os resultados do FAST.

Conclusão Final: Os resultados sugerem que o género, a cultura e as competências de memória de curto-prazo podem ter impacto na variabilidade nos relatos de dor induzida experimentalmente. Uma investigação mais aprofundada sobre estas relações revela-se necessária para uma melhor compreensão dos processos envolvidos na avaliação de intensidade de dor.

Palavras-Chave: características individuais; características demográficas; variabilidade nos relatos de dor; Digit Span; Dor

Abstract

Introduction: Pain is present in several diseases and has a significant negative impact on the quality of life. The difficulties in defining the concept, accurately reporting, and assessing pain has been considered the main reasons for the failure of clinical trials to evaluate the effectiveness of new analgesic medications. In this study it is explained the concept and history of pain, the neuromodulation and the ascending as descending pathways, the different types of classification of pain, the impact of the memory while processing pain, the most common forms of pain assessment, the way people perceive differently the pain and the impacts that individual variables have in reporting pain skills.

Objectives: This study is based on the following objectives: the differences in the experimental variability of FAST (measured through R^2 , ICC, CoV) in the two cultural studies (Portugal and Israel; to study a relationship between individual differences (measured through the comparative groups) and how differences in the variability obtained through the FAST (measured through the R^2 , ICC, CoV); to study a comparison between the demographic differences (age, sex, years of schooling, marital status, and BMI) and how differences in the accessible variability of the FAST (Mean of the R^2 , ICC, through CoV); and, using correlating the relationships between the last short-term memory capacity (measured through the Digit Memory task) and the experimental variability of FAST pain reports (measured from the R^2 , ICC, Cov).

Method: This retrospective study involved the analysis of the results of 452 healthy individuals to whom, in two laboratories, the focused analgesia selection test (FAST) was applied, which allows the measurement of variability in reports of pain induced by experimental stimuli. Demographic information (age, gender, education, civil status, BMI) and individual characteristics were obtained through the following questionnaires: SCS-R; PSQ; PCS; LOT; BAQ; HADS; MAIA. Furthermore, short-term memory was evaluated through the Digit Memory test.

Results: The collected data showed that there is high dispersion in the results of variability in pain reports. There are associations between gender, civil status and pain catastrophizing compared to the FAST results and some correlations were also found between Digit Span and the two study sites and with the FAST results.

Final Conclusion: The results suggest that gender, culture, and short-term memory skills may impact the variability in reports of experimentally induced pain. Further

investigation of these relationships is necessary for a better understanding of the processes involved in pain intensity assessment.

Keywords: Individual Variables; Demographic Variables; FAST; Digit Span; Pain

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1. Pain Introduction

1.1. Pain concept and history

The experience of pain is a fundamental body defensive mechanism and survival ability, to react towards a stimulus to avoid further damage. It's also a complex system, even the construct of pain is hard to define and has been different through time.

The first philosopher to use the scientific method, that developed in the 17th century, to propose an explanation to the question “What is pain?” was Descartes. He proposed that although humans have a soul (or mind), the human body is, yet, a machine, like an animal's body so it has to have a center of all, a control system. This concept impacts the history of experiments during the first half of the 17th century and it is marked by a search for specific pain fibers, existing pathways, and a pain center in the brain. The pain was interpreted as a specific, straight-through sensory projection system. This rigid anatomy of pain led to attempts to treat severe chronic pain by a variety of neurosurgical lesions and there was no room for psychological contributions to pain, such as attention, experience, and the meaning of the situation. Instead, pain experience was held to be proportional to peripheral injury or pathology. To thoughtful clinical observers, this theory was wrong therefore several attempts to find a new theory were done. Through time theories gradually evolved and the newer concepts moved the field in the right direction: into the spinal cord and away from the periphery as the exclusive answer to pain (Melzack, 1996). The contributions of psychological and emotional factors to the pain experience have been emphasized, becoming crucial variables in the development of a biopsychosocial approach as a persistent pain treatment. (Cornish & Cornish, 2020)

The definition of pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage” was defined by the International Association for the Study of Pain (IASP) but in 2019 they proposed a new one to describe the pain as “an aversive sensory and emotional experience typically caused by or resembling that caused by, actual or potential tissue injury”. This was ultimately accepted in 2020. In each definition is taken into consideration the emotional aspect of pain, and these emotions can be influenced by biological, social, and other psychological factors, so pain can be seen as a subjective experience.

Table I Pain as a disease: first usage of the term, features, and supporting evidences

	Bonica, 1953 ²	Bonica, 1990 ¹⁹	Raffaeli, 1992 ²¹	Cousins, 1999 ²³	Siddall and Cousins, 2004 ²⁴	Niv and Devor, 2004 ⁵
Term	Pathologic pain	Chronic pain	Pain as a disease	Chronic pain	Persistent pain	Chronic pain
Features	Pain deviating from the physiologic norm	Pain persisting beyond the usual healing course of an acute injury or disease, or the pain recurring at intervals for months or years	Dysfunction of the endogenous nociceptive system	Persisting pain causing physical effects involving the nervous system	Persistent pain entailing changes expressed in a specific constellation of symptoms	Autonomous disease with own symptoms and a specific tissue physiopathology
Evidences	Hypothesis grounded on clinical evidences	Clinical evidences	Hypothesis grounded on a theoretical idea and clinical evidences	Clinical cases and experimental studies	Literature review	Clinical and experimental evidences

Illustration 1 - Different terms to define pain through the years (Raffaeli & Arnaudo, 2017)

Niv and Devor, 2004 ⁵	Melzack, 2005 ²⁹	Cousins, 2007 ⁵⁰	Tracey and Bushnell, 2009 ³⁰	Dubois et al., 2009 ³²
Chronic pain	Chronic pain	Persistent pain	Chronic pain	Maldynia
Autonomous disease with own symptoms and a specific tissue physiopathology	The output of the body-self neuromatrix activating perceptual, homeostatic, and behavioral programs after injury, pathology, or chronic stress	A self-perpetuating condition which may be due to biologic, psychologic, and environmental factors	A condition characterized by a disordered nervous system	A neurologic condition characterized by pathologic changes in the nervous system
Clinical and experimental evidences	Experimental and clinical evidences	Literature review	Literature review	Literature review

Illustration 2 - Continue - different terms to define pain through the years (Raffaeli & Arnaudo, 2017)

1.2. Modulatory system of pain

Nowadays, it's known that pain is the result of the actions of numerous components of the nervous system. All over the body, several types of receptors for noxious stimuli exist, the nociceptors, and they can detect different types of stimuli, such as chemical, thermal, electrical, or mechanical sensations.

1.2.1. Nociceptors

Nociceptors are pain-specific receptors of primary sensory neurons (Bentley et al., 2018). The basic pain information undergoes three stages when a noxious stimulus is detected: transduction, transmission, and modulation. Transduction occurs when noxious information is captured by the nociceptors and is converted into chemical signals that are then changed into electrical messages in the neurons. After the completion of transduction, the transmission takes place bypassing the electrical events along the neuronal pathways. Lastly, modulation takes place at all levels of nociceptive pathways through the primary afferent neuron, dorsal horn, and higher brain centers by bottom-up or top-down regulation. All these lead to one end result: allowing us to feel the painful sensation triggered by the stimulus (Mun Fei Yam et al, 2018).

They can be characterized by the type of pain stimulation they conduct and their response to that stimulus as unimodal, responding to either mechanical or thermal stimulation, or polymodal, responding to thermal, mechanical, and chemical stimuli (Bentley, 2018). The main nociceptors responsible for the sensation and mechanism of pain are free nerve endings of sensory $A\delta$ and unmyelinated C nerve fibers, which respond to tissue damage.

1.2.2. Nerve Fibers

The pain mechanism relies on two types of nerve fibers, $A\delta$ and C, to transmit noxious information to the dorsal horn (DH) of the spinal cord. The fibers of Group A were classified by Erlanger and Gasser as myelinated fibers and are activated under thermal or mechanical stimuli. It can be further subdivided into $A\alpha$, $A\beta$, $A\gamma$ and $A\delta$, each with various feature sets. $A\delta$ -fibers are fast-conducting thinly myelinated fibers and result in immediate sharp and pricking pain. (Bentley, 2018).

Group C fibers are primarily functionally nociceptive, bringing sensory information and assembling about 70% of nociceptive information afferents, which then reaches the spinal cord. Both A and C fibers are mainly used in superficial organs, such as the skin, while C fibers are mostly supplied to other deep somatic structures, such as muscles and joints (Mun Fei Yam et al, 2018). Because they are slow-conducting unmyelinated fibers the activation of C-fibers is stimulated by thermal, mechanical, or

chemical stimuli, which often results in poor localization and dull pain sensation (Aronoff, 2016).

1.2.3. Ascending pathways

So how does the message get to the brain? The answer is through the ascending pathway of pain. Prostaglandins (PG) are an important stimulus in the ascending pathway that usually responds to any inflammation. The sensory nerve fibers will synapse with the prostaglandin and get the feedback information through the first-order neuron until it gets to the dorsal horn (ganglia) of the spinal cord. Here the information crosses to the other side of the body, more specifically, the start of the second-order neuron, and this mechanism constitutes the spinothalamic tract. The very end of the second-order neuron ascending pathway is the thalamus. From there will the information be spread to several brains areas that can be conceptualized in two fundamental systems: the lateral pain system, which mainly involves the activation of the secondary somatosensory cortex and posterior insula, and it constitutes the system related to the sensorial component of pain (being able to describe the intensity, location, and characteristics of pain); and the medial pain system that is related to the activation of two main areas, the anterior cingulate cortex, and the anterior insula. It is also related to the unpleasantness of the pain (the emotions related to this experience - the affective-motivational component of pain which signals the unpleasant quality of the experience) and enables the autonomic activation that follows a noxious stimulus (the classic fight-or-flight reaction) (Purves, 2004). It was based on this area that the existence of a pain matrix was considered. For a practical example, if the pain is in the right hand, the third-order neuron will project it in the left secondary somatosensory cortex, in the area responsible with the hand pain perception, and it will also project to the medial pain system setting a discomfort response to the body. Although, along the way, it also activates several brainstem nuclei, as the periaqueductal gray (PAG which is responsible for the modulation and process of pain, and also projections with cortical and subcortical areas), nucleus tractus solitarius, dorsal reticular nuclei (whence pain signals from the lower body reach the cerebral cortex), among others. (Apkarian et al., 2005; Parhizgar & Ekhtiari, 2018).

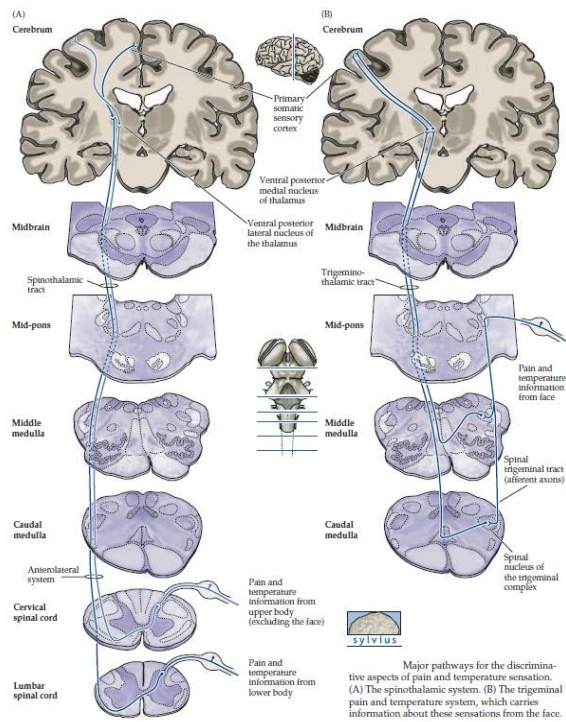


Illustration 3 - Sylvius, Ascending pathways.

1.2.4. Descending Pathway

But now the intriguing question is, what does the brain do with the information? How does the perception of pain resolve in a response to it? And the answer is through the descending pathway of pain which originates in central structures of the nervous system, project to the dorsal horn of the spinal cord, more specifically by passing along the periaqueductal gray matter and then the nucleus raphe magnus, where they facilitate or inhibit via the serotonergic noradrenergic neuron and thus regulate pain signals going up to the brain (Purves, 2004). If the response is excitatory means that there's an activation of recurrent loops through the brainstem reinforcing the ascending pathways from the spinal cord an resulting in more pain perception. If the response is inhibitory the descending noradrenergic input to the spinal cord from the dorsolateral pons activates on the spinal nociceptive mechanisms stopping the chain of pain perception (High, 2008). Briefly, the descending pain modulatory system essentially includes hypothalamus and brainstem structures such as the PAG and rostral ventromedial medulla, controlled by prefrontal, anterior cingulate, and insular cortices (Wiech et al., 2008).

1.2.5. Gate Control Theory

Patrick David Wall and Ronald Melzack, in 1965, were the first to hypothesis that pain is due to patterns of nerve impulses rather than straight-line transmission of

modality-specific impulses to a pain center, which led to explaining the difficulties in the correspondence between stimulation intensity and pain intensity. They assumed that information that arrived at the spinal cord was filtered and selected on the basis of the total pattern of activity in stimulated fibers as well as by descending information from the brain and that the spinal cord functioned as a gate, filtering the pain inputs, modulating the pain experience, increasing or reducing it.

Then, in 1996, Melzack proposed that the gate control theory of pain was based on the following propositions:

1. The transmission of nerve impulses from afferent fibers to spinal cord transmission (T) cells is modulated by a spinal gating mechanism in the dorsal horn.

2. The spinal gating mechanism is influenced by the relative amount of activity in large-diameter (L) and small-diameter (S) fibers: activity in large fibers tends to inhibit transmission (close the gate) while small-fiber activity tends to facilitate transmission (open the gate).

3. The spinal gating mechanism is influenced by nerve impulses that descend from the brain.

4. A specialized system of large-diameter, rapidly conducting fibers (the central control trigger) activates selective cognitive processes that then influence, by way of descending fibers, the modulating properties of the spinal gating mechanism.

5. When the output of the spinal cord transmission (T) cells exceeds a critical level, it activates the action system-those neural areas that underlie the complex, sequential patterns of behavior and experience characteristics of pain.

The theory's focus on the modulation of inputs in the spinal dorsal horns and the brain's complex role in pain processes had both a clinical and a scientific influence. Psychological causes previously dismissed as "reactions to pain;" were now seen to be an important part of the treatment of pain, and new avenues were opened for pain management (Melzack, 1996).

1.3. Pain classifications

According to the International Association for the Study of Pain (IASP), pain can be classified, based on the region of the body involved (e.g., head, visceral), the pattern of occurrence's duration (acute and chronic), or the system of which dysfunction that may cause the pain (e.g., gastrointestinal, nervous). Thus, pain internationally has been classified into three major classes - nociceptive, neuropathic, and inflammatory pain

based on three characteristics symptoms, mechanisms, and syndromes (Orr et al., 2017, p. 416).

1.3.1. Neuropathic pain

Neuropathic pain is generally defined as nerve damage or weakening of the nerve, and allodynia is also associated with it. Allodynia is a central pain sensitization that is a result of repetitive non-painful stimulation of the receptors. This causes a pain response from a stimulus that is considered in normal circumstances to be non-painful due to the sensitization process from the repetitive stimulation. This condition may be described as "pathological" pain, as neuropathic pain does not necessarily serve any function in terms of our body's protection mechanism, and the pain can be in the form of constant sensation or episodic events. The primary causes of this type of pain may be generally triggered by inflammation or metabolic diseases, such as diabetes, trauma, toxins, tumors, primary neurological diseases, and herpes zoster infection (Chaudhuri et al., 2015). Neuropathic pain can be caused by the damage of the nerve (like to the back, leg, or hip problems or injuries) affecting the somatosensory nervous system and may be generated by the disorders of the PNS or CNS but injuries to tissue, muscles, or joints are an uncommon cause. The neurochemistry of the damaged axons can be altered due to the initiations of complex reaction upon compression, stretching, or transaction of the periphery nerves, followed by a spontaneous hyper-excitability on the site (Yam et al., 2018). Although the injury may heal, the nervous system damage may not. As a consequence, for several years after the accident, the person can suffer constant pain.

1.3.2. Nociceptive Pain

Nociceptive pain is the most common type and consists of the response of our bodies' sensory nervous systems towards actual or potentially harmful stimuli being detected by nociceptors, responsible for the first stage of pain sensations. There are two types of primary afferent nociceptors (nerve fibers) responding to noxious stimuli displayed in our bodies. Both these nociceptors have specialized free nerve endings that are widely located in the skin, muscle, joint capsule, bone, and some considerable internal organs allowing us to feel pain from short-lasting-pricking to stronger pain. They are functionally used to detect potentially damaging chemical, mechanical and thermal stimuli that might put us in jeopardy. The major nociceptive pain can be categorized into three types, such as visceral, radicular, and somatic pain (which is further classified

into two kinds: deep somatic and superficial pain). There are three dominant roles for the receptors in the primary afferent neurons, which are excitatory, sensitizing, and inhibitory response. Once these receptors are being stimulated and have reached the pain threshold, the resulting impulses are propagated along the afferent fibers towards the DH (PNS) and medulla (cranial) (Yam et al., 2018). A good example of nociceptive pain is the pain felt when a person breaks an ankle. It tends to go away as the affected body part heals.

1.3.3. Duration

The definitions of the pain classification system represent the duration of time the patient experiences pain in hours, months, or years. The two main classifications based on the duration are acute and chronic pain.

- *Acute pain*

Acute pain is often related to acute injury or trauma and acts as a warning system in the body that something is wrong, and the resolution of acute pain results from tissue healing or repair. It is also classified as a short-term pain that resolves within three to six months. It can be described as sharp, stabbing, tight, burning, aching, or throbbing sensation, more especially, is typically characterized by relatively discrete neuroanatomic pathways mediating effects of the somatic injury; the transmission of information with survival value that initiates protective physiological mechanisms (against injury extension) and signals the need for corrective action to promote healing; a time-limited course during which treatment is aimed at correcting the pathological process; and the relative absence of marked psychosocial changes or behavioral changes disproportionate to pain intensity (Michaelides & Zis, 2019; Martelli, Grayson, and Zasler, 1999). Neurologically physiologic changes can occur, resulting in peripheral and central sensitization. Health care professionals must aim to achieve optimal pain management outcomes because acute pain that persists can transition to chronic pain, otherwise known as “pain chronification”. For good long-term patient outcomes, suitable and timely pain relief treatment is therefore necessary. Genetic and psychological responses also play a role in pain chronification (Orr et al., 2017).

- *Chronic pain*

Currently, chronic pain is characterized as persistent or intermittent pain that continues beyond the expected tissue healing period, commonly associated with various

disease processes, including psychological conditions. It is usually long-term pain, 3 months or longer, and is more likely to be characterized by relatively ambiguous neuroanatomic pathways mediating somatic effects; transmission of information that may perpetuate protective responses of limited adaptive value especially to the extent that there is a lack of underlying tissue damage and/or decreases in, or avoidance of, activity, inhibiting rehabilitation; a protracted course of medication use and minimally effective medical services; and marked behavioral and emotional changes, including restrictions in daily activities.

The reason why there are so many cases of ineffectively treated chronic pain is likely to result in a cyclic disability-enhancing pattern of further decreased activity and avoidance that prevents normal restoration of function and perpetuates painful experience is often an avoidant behavior to the therapeutic and reduced activity level. The longer pain persists, the more recalcitrant it generally becomes and the more treatment goals focus on coping with pain and its concomitants (Hart et al., 2000).

Chronic pain is a significant medical and social issue. Pain affects everyone: patients, families, workforce, and all populations in society.

1.3.4. Inflammatory Pain

Inflammation is a normal biological reaction developed by the tissues inside our body in order to remove the necrotic cells and begin the tissue repair process as a reaction to damaging stimuli. Neutrophils are normally the first responders to an inflammatory response and accumulate from the bloodstream at the site of injury, followed by the release of additional chemical mediators. Inflammation can lead to three main reactions: hyperalgesia, allodynia, and sympathetic maintained pain (Yam et al., 2018). Also, there are four possible outcomes of inflammation: total resolution, fibrosis, abscess formation, or chronic inflammation.

1.4. Pain perception

Pain can be perceived differently from person to person which means not only physiological processing of the nociceptive signal but conscious comprehension and awareness of the unpleasant stimulus can be changed by several "environmental" influences, along with psychological and personality-related factors such as previous pain experiences, emotionality and cognition, somatization and catastrophizing, presence of

acute and chronic stressful life events, fatigue, anxiety, fear, boredom and anticipation of more pain, as well as socioeconomic factors (e.g., social support, acceptance, incentives, education, occupation and quality of life). Furthermore, pain behavior is different among genders, ethnicities, and age which contribute to a wide inter-individual variance (Belfer, 2013). Pain also produces an emotional reaction, not just a physical one. Some pain can be caused by grief or depression but are not easy to measure or to classify (Odendal, 2010).

1.4.1. Neuropsychological Profile

Experiencing pain can cause cognitive impairment, particularly in the chronic pain community, and is a significant obstacle to everyday activities and recovery. Patients' main complaints are "forgetfulness" and lack of concentration. However, several related factors make it difficult to characterize and understand these problems in chronic pain, such as sleep disturbances, depression, different types of medication, heterogeneity of the population in the study, several cognitive components, and different ways of evaluating (Turk & Gatchell, 2002). These changes tend to be linked to neural networks that are known to present neurochemical and functional structural changes in chronic pain and that are common to both pain and cognition (Wiech et al., 2005). Hart et al, in 2000, mentioned that the most consistently identified cognitive changes in pain patients occur in attentional capacity, processing speed, and psychomotor speed.

1.4.2. Neuroimaging Studies

Studies using neuroimaging techniques, including electroencephalography (EEG), magnetoencephalography (MEG), functional magnetic resonance imaging (fMRI), and positron emission tomography (PET), have highly led our understanding of the neuroanatomical relationship between pain and cognitive processing. The six brain regions most commonly activated during pain processing are two of the somatosensory cortical areas, the insular cortex (IC), the thalamus, the prefrontal cortex (PFC), and the anterior cingulate cortex (ACC) (Apkarian et al., 2005). The periaqueductal gray (PAG), basal ganglia, cerebellum, amygdala, and hippocampus have also, though less consistently, shown pain-related activation. The ACC receives input from limbic regions such as the thalamus, hippocampus, and amygdala, and fMRI has been used to demonstrate its function in regulating selective attention, working memory, and error

awareness (Jurik et al., 2015). But there is still a need, for further functional imaging studies examining brain activation in chronic pain patients carrying out cognitive tasks.

1.5. Pain assessment

As stated before in enormous case studies and experiments assessing pain accurately is very harder due to the subjectivity of the concept. This problem has significantly impacted the economy. In our country, the direct and indirect costs of health care associated with pain are very high, with hospitalization being the largest component of direct costs and social benefits the largest share of indirect costs so it's critical to understand better pain to consequently be y treated better.

To assess pain levels in health care treatments clinicians use various forms. The two methods used the most are observational and self-report methods. The observational method includes behavior evaluation like posture and facial expression, function assessment like mobility, and also vital sign appraisal through respiratory and pulse rate, blood pressure, and others. The other are self-report tools for pain measurement like numerical rating scale (NRS), the visual analog scale (VAS), and the verbal rating scale (VRS). In the NRS the patients rate their pain intensity ranging from “0”, “no pain”, to “10” (or 100), “the worst pain imaginable” by specifying the number that best suits their perceived pain (Brooker et al., 2011). The visual analog scale (VAS) consists of a horizontal line marked 0 and 10 or 0 and 100 at its edges and the patients mark their level of pain (Chapman & Kirby-Turner, 2002). The verbal rating scale (VRS) presents certain adjectives to the patients to help them describe the level of pain intensity. They are mostly four to six adjectives, starting with “no pain” and ending with “extremely severe pain” (Breivik et al., 2008). All of these measures are considered uni-dimensional scales and are used to evaluate in an experimentally induced laboratory test. Still, in the self-report methods, there are also multidimensional scales to assess pain and the impact on physical, emotional, and social functions like the Brief Pain Inventory (BPI, Cleeland & Ryan, 1994).

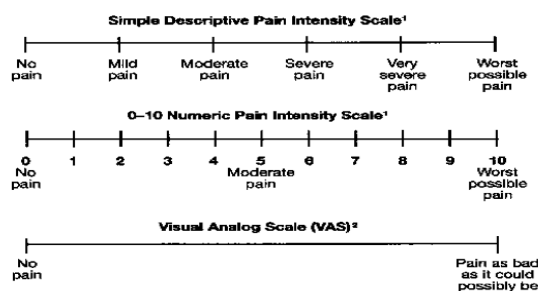


Illustration 4 - Commonly used one-dimension scales (Kishner et al, 2018, Pain Assessment)

As is stated before, there are several paradigms for assessing induced pain using painful stimuli in laboratory with controlled settings under the use of standardized methods. These models give us three most common outcomes: pain threshold, tolerance, and intensity. Pain threshold is used to explore the sensitivity of the tissue to specific pain stimulation modalities. According to the IASP: the pain threshold is a personal experience and it refers to the minimum amount of pain a person can recognize while receiving the stimulus ("IASP Terminology - IASP", 2018). Pain tolerance is also used to explore sensitivity by using another subjective experience and it refers to the maximum level of pain that the subject can endure while receiving the stimulus ("IASP Terminology - IASP", 2018). Finally, pain intensity is often collected by applying a stimulus and asking the individual to rate his pain using the VAS or NRS. In conclusion, all these methods can obtain data regarding sensitivity. In addition to the sensitivity, it is also possible to study the variability of pain.

Scales typically used to analyze pain for adolescents and adults by Patty Montgomery and colleagues (2017):

- Numeric Pain Rating Scale
- Verbal Descriptor Pain Scale
- FACES Pain Scale, revised
- Wong-Baker FACES Pain Rating Scale
- Iowa Pain Scale
- Functional Pain Scale
- Critical Care Pain Observational Tool
- Brief Pain Inventory
- McGill Pain Assessment Tool

And also, for Nonverbal or cognitively impaired individuals:

- Adult Nonverbal Pain Scale
- Checklist of Nonverbal Pain Indicators
- Pain Assessment in Advanced Dementia Scale.8

1.5.1. Placebo Effect

The placebo effect is defined as a physiological response following the administration of a pharmacologically inert “remedy.” The word placebo means “I will

please,” and the placebo effect, in medicine, has a long history of use (and abuse). Most notably, this placebo effect could be blocked in postoperative patients by naloxone, a competitive opioid receptor antagonist, indicating a substantial pharmacological basis for pain relief. A common misunderstanding about the placebo effect is the view that patients who respond to a therapeutically meaningless reagent are not suffering real pain, but only “imagining” it, this is certainly not the case, the placebo effect is quite real (Purves, 2004).

1.6. FAST

The focused analgesia selection test (FAST) is a laboratory psychophysical method that consists of recording subjects’ pain reports in response to repeated administration of thermal noxious stimuli of various intensities applied on the ventral surface part of the non-dominant arm with the Medoc® Thermal Sensory Analyzer II (Medoc TSA II). “Variability” means being likely to change often with a standard measurement and “accuracy” means the ability of being exact or in other words the agreement of a particular measurement with an accepted standard. Using this method, the subjects that have low variability, which means that give similar ratings under the equal stimulus intensity are discriminated/separated to those that have high variability skills, meaning that they give different ratings under the equal stimulus intensity.

The procedure consists in raising the temperature from a baseline of 32°C, letting it peak for 3 seconds at 1 of 7 designated temperatures (43°C, 45°C, 47°C, 48°C, 49°C, 50°C, or 51°C), and then decrease it down to the baseline. These thermal noxious stimuli are done 49 consecutive and random times and last precisely 8 seconds each. The subjects are asked to rate the peak pain intensity of each stimulus by using a numerical scale from 0= “no pain” to 100= “worst pain imaginable”. Stimuli were triggered in 10-20 second intervals allowing the subject sufficient time to rate the pain they perceived during each stimulus. The location of the thermode is adjusted every 10 stimuli to minimize sensitization and/or habituation effects. The application of the full procedure takes around 20 minutes (Treister, Eaton, Trudeau, Elder & Katz, 2017).

The FAST procedure has three important outcome measures to take into consideration, the coefficient of determination (R^2), the Intraclass Correlation Coefficient (ICC), and de Coefficient of Variance (CoV). The R^2 is calculated by a power model regression and measures the function between the real intensity of the stimuli and the intensity reported by the subject. If the subject’s ratings are in correspondence with the intensity of the stimuli (that is, every time the subject gives a high rating for a high

stimulus intensity and gives a low rating for a low stimulus intensity), the R^2 will be higher and the subject will be considered accurate. On the other hand, if there is low correspondence between the ratings of the subject and the intensity of stimuli, then the subject will be considered less accurate. The ICC is considered a good measure of reliability and uses a statistical 2-way mixed model, which indicates the ratings for each of the 7 stimuli of any of the 7 intensities are compared within each subject. So, if a subject has a high value (approaching 1) for ICC it means that their responses are similar each time the same temperature is applied. The CoV is the ratio of the SD to the mean. The average CoV was calculated as the mean of 7 CoVs, 1 at each stimulus level. A higher CoV demonstrates a larger variability in reporting. (Treister, Eaton, Trudeau, Elder & P Katz, 2017) (Khallouf, 2019).

In the first study that tested the validation of the FAST Treister and his colleagues assessed subjects with osteoarthritis of the hip, knee, and/or ankle using the FAST procedure. After, the patients were asked to make an exercise (stairs climbing) that was supposed to increase pain. Using FAST it was found that pain reporting accuracy varied between the different subjects and also one of the outcomes measures, the ICC, predicted significantly the change in clinical pain and the clinical results in the exercise tasks. Accordingly, the more accurate patients rated the expected increase in pain after the exercise. Summing up, they demonstrated that the use of FAST could give the ability to discriminate the subjects who are more accurate in reporting their pain changes from those with lower accuracy in pain reporting. The authors also used a task similar to FAST but using non-noxious stimuli instead of noxious and they were able to show that only FAST predicted the changes, thus showing that FAST results were pain-specific (Treister, Eaton, Trudeau, Elder & Katz, 2017).

In a second study (Treister et al, 2018), the same team created the Accurate Pain Reporting Training (APRT). It consists of pain reporting training using the application of the mechanical stimuli of the FAST procedure. As in FAST varying intensity, stimuli are applied several times and after the subjects rated each stimulus, feedback is given concerning the response on pain rating accuracy of the subjects. Patients with painful diabetic neuropathy (PDN) were assessed underwent a controlled two-stage randomized trial. In the first part, the training stage, the subjects were randomly allocated to treatments (Training and No-Training), and the purpose of this stage was to determine whether or not the training method could increase the accuracy of pain reporting. Then, in the second part, the evaluation stage, participants were randomized into a double-blind crossover

trial of Pregabalin (PGN), and it was intended to determine whether the (APRT) system will impact the placebo effect and also it affects the sensitivity of the study test. As a result, the study showed a relationship between pain reporting variability (maybe driven by variance in error) and the placebo responses, concluding that the training stage increases the reporting accuracy of the subjects and lowers the placebo effect observed in the cohort (Treister et al., 2018).

In 2019 Treister and his colleagues took a deeper look at their previous study about a double-blind, placebo-controlled, clinical trial of naproxen vs placebo in patients suffering from osteoarthritis (OA) of the knee to explore if the pain variability was related to the placebo response. To do so they analyzed the moderate linear relationship between variability of clinical and the experimental pain reports to see if it was statistically significant and detected that both correlated with the placebo response, but only the FAST predicted the treatment difference between naproxen and placebo, showing that FAST predicted preferential placebo responsiveness. Based on these findings, the authors discuss a theoretical model that suggests that individuals who are more focused on internal cues report their pain more accurately (low clinical pain variability and low placebo response) than the individuals who are more focused on external cues (therefore present inaccurate pain reports, large clinical pain variability, and high placebo response) (Treister et al., 2019).

1.7. The impact of individual differences reporting pain

As it was said before pain is a subjective experience and the sociocultural factors may be the answer for the reason that two people with the same injury can experience different levels of pain or even no pain at all with the same kind of injury on the body. Regardless of any previous study, it remains unclear what mechanisms and what differences may justify differences in the performance of FAST. Sociodemographic variables may be the answer, maybe different age, gender, culture (race/ethnicity), and education have a different impact on pain variability and clinical pain expression. Although there's a lot of studies and interest in this area, the majority are specifically about chronic pain. More reviews about acute pain are needed.

1.7.1. Age

Puberty seems to be the first step to finding differences in pain perception. There is no sex disparity in prevalence before puberty in many clinical pain situations, but an

increased prevalence in one sex or another (usually women) after puberty is seen. Some pain disorders decrease in intensity after the fourth decade of existence, such as migraine headaches and TMD, while others, such as interstitial cystitis, joint pain, and fibromyalgia, tend to persist until later in life (Greenspan et al., 2007). A study of Ostrom et al., in 2017 slightly indicates that general pain sensitivity tended to decrease with age. Also, advancing age is associated with increased persistent pain, although this seems to plateau after the age of 70 years. (Quiton et al., 2020)

1.7.2. Gender

Of these, regarding the most investigated concept, “pain sensibility”, gender differences have been the most frequently studied, and most of the literature describes greater pain sensitivity for women versus men. However, the mechanisms are still unknown. Although women generally respond to noxious stimulation with a greater report of pain than men, the difference is small. In contrast, women suffer a disproportionately greater number of pain disorders and dominate those pain disorders by a large margin relative to men. However, a link from increased pain sensitivity in women to the increased prevalence of pain disorders in women is plausible, the relatively small difference in pain sensitivity makes that link improbable. A good example of a study that takes the other variables into consideration was done by Ostrom and her colleagues (in 2017), using demographic predictors of pain sensitivity that they take advantage of a previous study done by Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) and evaluated the association between gender, age and race with 34 different measures consisting in pressure, mechanical and thermal pain. They concluded that women were significantly more pain-sensitive than men, that age had a really small effect (but also their range was 18-44 years). The study conducted by Quiton et al., in 2020, where 1173 participants were analyzed by their pain disparities based on race, age, sex and socioeconomic status had the same outcome, that chronic pain is more prevalent in women than in men; women also experience more daily pain and are at greater risk of developing severe pain after medical procedures compared to men.

1.7.3. Culture

The effect of culture on gender-specific responsiveness to experimental pain or the presentation of clinical pain conditions has been explored in a few research studies. Sociocultural mechanisms, or perhaps racial differences, would be indicated by cultural

differences in gender-specific pain patterns, whereas similarities across cultures would indicate biological or biopsychological mechanisms (Greenspan et al., 2007).

A study about the influence of patient pain race, done by Miller and her colleagues in 2020, propositioned a significant main effect indicating Black patients rated as more distressed and were more interfered by their pain than White patients. Ratings of patients' reactions to pain did not significantly differ by culture/race. So, future cross-cultural studies could be useful for illuminating mechanisms underlying. Also, the Ostrom et al., 2017 study discovered variances with different race/ethnicity pain results varied within the group, specifically that Non-Hispanic white individuals were less pain-sensitive than African-American, Hispanic, and Asian individuals.

1.7.4. Education

There are no studies with statistically significant results to draw conclusions about the impact that education has on pain variability, mainly on pain sensitivity, which is why it is important to better explore this field. However, there is a study regarding the US that reported that greater levels of completed schooling are correlated with lower pain prevalence (Zajacova et al., 2020).

1.8. Pain memory

The memory can be divided by short-term memory (STM - capacity to keep a small amount of information in mind in an active, readily available state for a short period of time) or long-term memory (LTM - the storage of information over an extended period of time). Also, by episodic memory (the conscious recollection of a personal experience that contains information on what has happened and also where and when it happened) or semantic memory (refers to the memory of meaning, understanding, general knowledge about the world). People with chronic pain frequently experience deficits in working memory (WM), which is included in the short-term memory, and other cognitive domains. WM is a sort of memory that temporarily retains and rehearses relevant information – WM can control the extent to which attention is captivated by irrelevant distracters and maintains the properties of relevant information (International Association for the Study of Pain, 2021). The few imaging studies that looked at the neural correlates of STM of pain intensity and location, showed an involvement of fronto-parietal cortices generally involved in WM as well as some core pain-related regions (e.g. primary somatosensory cortex, insula). This is consistent with the idea that cortices engaged in

perceptual coding of basic sensory properties are also involved in short-term memory retention (Khoshnejad et al., 2017). Pain and working memory (WM) deficits are bidirectional linked and that link is well-documented but poorly comprehended. In contrast, similar cognitive deficits have been observed in healthy individuals that are undergoing an experimental pain task. (Procento et al., 2021)

In several diseases in which chronic pain is a symptom, memory impairments have been shown, especially prevalent in Fibromyalgia. Memory studies of patients suffering from chronic pain have largely examined working (explicit) memory parameters. Implicit (procedural, semantic, and conditioned) memory is usually considered an automatic mechanism, less likely to be impaired by the experience of chronic pain (Grisart & van der Linden, 2001). Nevertheless, in semantic memory tasks, FM patients often displayed deficits where they were required to select the antonym or synonym of a word presented. In FM, fatigue and depression are also normal, and in these cognitive domains, they can affect performance (Mc Connolly, 2000).

The relationship between these characteristics and variability of pain is unknown and the vast majority of studies are on sensitivity to pain and almost nothing on variability of pain. Hence, it is for this reason that this research will be carried out.

2. Aims of the study

The aim of the current retrospective and correlational study is to investigate individual differences that may be related to pain reporting variability using data from studies in healthy individuals from two different laboratories, located in different countries (PT and ISR). Since currently, there is sparse information concerning FAST mechanisms, this study will assess the correlations between individual differences traditionally related to pain sensitivity (such as age, sex, cultural origin, and educational as well as individual characteristics, measured by questionnaires) with experimental within-subject pain variability (measured by the FAST outcome measures, R^2 , ICC, and CoV). Another aim is to correlate short-term memory (measured by the Digit Span) and this within-subject experimental variability. The study of within-subject pain variability is at its beginning therefore this study is exploratory. There is currently a lack of literature concerning the pain variability, mostly in healthy individuals, thus limiting the ability to have a grounded hypothesis.

The main objectives of the current study are:

Objective 1: To compare the differences in the experimental within-subject variability in pain intensity reports (measured by FAST outcomes R^2 , ICC, and CoV), in two different cultural groups (Portugal and Israel).

Objective 2: To correlate demographic characteristics (age, gender, years of education, civil status, and BMI) with the experimental within-subject variability of pain (measured by FAST outcomes R^2 , ICC, and CoV).

Objective 3: To explore the relations between individual differences measured by questionnaires (SCS-R; PSQ; PCS; LOT; BAQ; HADS; MAIA) and the experimental within-subject variability of pain (measured by FAST outcomes R^2 , ICC, and CoV).

Objective 4: To correlate the relations between short-term memory abilities (measured by the Digit Span Task) and the experimental variability of pain reports (measured by FAST outcomes R^2 , ICC, and CoV).

3. Method

3.1. Participants

520 subjects were recruited by 8 studies both in Israel and Portugal. From this sample, 29 subjects from the fibromyalgia study, 33 subjects from the dancer's study, and 6 subjects from the FAST, FM, and HC studies were excluded to form a healthy general population representation. Thus, the final cohort consisted of 452 subjects, 352 from Israel and 100 from Portugal.

3.2. Instruments

Demographic Information: Demographic questionnaires includes questions such as age, gender, educational level in years, civil status, and the body mass index.

FAST: The procedure consists in raising the temperature from a baseline of 32°C, letting it peak for 3 seconds at 1 of 7 designated temperatures (43°C, 45°C, 47°C, 48°C, 49°C, 50°C, or 51°C), and then decrease it down to the baseline. These thermal noxious stimuli are done 49 consecutive and random times and last precisely 8 seconds each. The subjects are asked to rate the peak pain intensity of each stimulus by using a numerical scale from 0= "no pain" to 100= "worst pain imaginable". Stimuli were triggered in 10-20 second intervals allowing the subject sufficient time to rate the pain they perceived during each stimulus. The location of the thermode is adjusted every 10 stimuli to minimize sensitization and/or habituation effects. The application of the full procedure takes around 20 minutes (Treister, Eaton, Trudeau, Elder & Katz, 2017).

Digit Span - This task consists of two parts and requires subjects to repeat a series of digits of increasing length. Digits forward (Part A) is administered first and requires the repetition of digits in the same order presented. An example of a given instruction is: "I'm going to tell you a sequence of numbers and when I finish saying them you will repeat them in exactly the same order". This task is a good measure of simple attention. Digits backwards (Part B) participants must repeat digits in inverse order and is a qualitatively different type of task that relies more upon working memory skills. The score obtained in the test corresponds to the largest number of digits that the subject was able to recall correctly, with the total score being the sum of the two components - direct and inverse. (Reynolds, 1997).

Questionnaires'/Scales:

Self-consciousness scale revised version (SCS-R) - The Self-Consciousness Scale by Fenigstein, Scheier, & Buss developed in 1975 is a 23-item questionnaire, which measures individual differences in private and public self-consciousness and social anxiety. The revised version changed the original one so that the language used is more accessible for a very broad population rather than just psychology students, who are often recruited for psychological test validation (Scheier et al., 1985). An example of a public self-consciousness question is: "I often check the way I look." Using a scale from 3 to 0 to answer being 3= a lot like me, 2= somewhat like me, 1= a little like me, 0= not at all like me.

Perceived Stress Questionnaire (PSQ) - This questionnaire consists of 30 items and was developed as an instrument for assessing the stressful life events and circumstances that tend to trigger or exacerbate disease symptoms. (Shahid et al., 2012) An example is: "You feel frustrated". Using a scale from 1 to 4 to answer being 1=Almost Never, 2=Sometimes, 3=Often, 4=Usually.

Life Orientation Test (LOT) - This is a standard psychological tool for measuring optimism and pessimism. The original version was created by Michael Scheier and Charles Carver in 1985 and consists of 12 questions. Then underwent a few revisions as an improved version to LOT-Revised (LOT-R). One example of the 12 questions is: "In uncertain times, I usually expect the best". A scale from 0 to 4 (being 0= Strong Disagree, 1= Disagree, 2= Neutral, 3= Agree and 4= Strongly Agree) must be used to answer.

Pain Catastrophizing Scale (PCS) - This scale was developed to help quantify an individual's pain experience, asking about how they feel and what they think about when they are in pain. Pain catastrophizing is characterized by the tendency to magnify the threat value of a pain stimulus and to feel helpless in the presence of pain, as well as by a relative inability to prevent or inhibit pain-related thoughts in anticipation of, during, or following a painful event. Higher scores are associated with higher amounts of pain catastrophizing (Sullivan, 1995). An example of an asked question is: "I anxiously want the pain to go away" and the participant must answer with a scale beginning with "0 = not at all" to "4=all the time".

Body Awareness Questionnaire (BAQ) - This is an 18-item scale designed to assess self-reported attentiveness to normal nonmotive body processes, specifically, sensitivity to body cycles and rhythms, ability to detect small changes in normal

functioning, and ability to anticipate bodily reactions (Shields et al., 1989). An example is: “I notice specific bodily reactions to being over hungry.” And the participant selects a number from 1 (being 1= “Not at all true of me”) to 7 (being 7= “Very true of me”) to answer.

Hospital Anxiety and Depression Scale (HADS) - This scale assesses the contribution of mood disorders, especially anxiety and depression in patients during medical practice (Snaith, 2003). It is a brief instrument commonly used to assess anxiety and depression in physically ill populations (Zigmond & Snaith, 1983). It has 14 items answered on a 4-point scale, from 0 to 3. Based on these items, two subscales can be obtained: Depression (7 items) and Anxiety (7 items). Scores can range from 0 to 21 in each subscale. A higher score indicates higher depression and/or anxiety. The validated Portuguese version of this instrument was considered adequate and was used (McIntyre, Pereira, Soares, Gouveia & Silva, 1999). An example is “I feel tense or ‘wound up’” and a scale from 0 to 3 (being 0=Not at all, 1=From time to time, occasionally, 2=A lot of the time, and 3=Most of the time) must be used to answer.

Multidimensional Assessment of Interoceptive Awareness (MAIA) – This is a multidimensional self-report measure of interoceptive body awareness through 32-item that assesses eight dimensions: noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body listening, and training. An example of this scale is: “I notice when I am uncomfortable in my body”. To answer must choose from a scale from 0 (equals “never”) to 5(equals “always”).

3.3. Procedure

This study consists of a retrospective analysis of data previously collected in 8 studies carried out in different laboratories both in Portugal and in Israel. The procedure of the studies in question followed a similar approach based on an initial collection of demographic data, followed by the application of individual assessment questionnaires and later on the cognitive task (specifically the Digit Span) and, finally, the application of FAST.

The data was already collected and stored through Excel (Microsoft Corp, Redmond, WA, USA) by the lead authors of the studies and was analyzed through the SPSS software system version 23 (IBM Corp., 2015, Chicago, IL, USA).

3.4. Statistical Analysis

Descriptive statistics will be used to present general characteristics and information, such as mean, median, and std. deviation. After, the Shapiro-Wilk test results will be analysed to see if all the variables follow, or not, a normal distribution. Since the the main variables of the study are non-normally distributed the non-parametric test will be applied such as the Mann-Whitney test for all nominal and ordinal variables and chi-square for scales variables. Lastly, the Spearman Correlation test will be applied between non-normally distributed variables (FAST vs Digit Span). Statistical significance will be defined as $\rho \leq .05$.

4. Results

The analysis of the results was based on the four main measures: demographic variables, individual variables related to the different scales/questionnaires applied, the results obtained from the FAST, and the results of the application of Digit Span. Thus, a statistical analysis was carried out on all the evaluation variables, in order to test the previously mentioned objectives.

4.1. Participants' Characteristics

The sample consisted in consisted of 452 subjects, 352 from Israel and 100 from Portugal (Table 1). For the total sample (PT and ISR), 203 subjects were male (44.9%) and 249 were female (55.1%) with mean and standard deviation of age: 24.93 ± 5.70 , ranging between 18 and 53 years old. Regarding the educational background, 0.7% of the subjects have the 9^o grade, 26.1% did gain a high school education. 71.9% followed a higher education of 98.7% - 6 subjects had missing information. The majority of them were single (86.5% of 98.9% - 5 subjects had missing information). The average and std. deviation of the B.M.I. scale is 23.18 ± 3.84 .

Table 1 - General Sample Characterization.

Total group		N	Mean	Median	Std. Deviation
Age		452	24.93	23.00	5.70
Years of Education		446	14.42	15.00	1.92
Body Mass Index		381	23.18	22.60	3.84

		Frequency	Percent	Valid Percent	Cumulative Percent
Gender	male	203	44.9	44.9	44.9
	female	249	55.1	55.1	100.0
Civil Status	single	391	86.5	87.5	87.5
	married	48	10.6	10.7	98.2
	divorced	4	0.9	0.9	99.1
	widow	1	0.2	0.2	99.3
	living together	3	0.7	0.7	100.0

Table 1 - N, mean, median, std. deviation, frequency, and percentage in the general sample

4.2 Individual differences

To evaluate the individual differences the mean, median, standard deviation, and frequency was analyzed, separately for each country, for the demographic, and the individual questionnaires.

Table 2 – Demographic information and individual differences, measured by the questionnaires, from Portuguese participants.

PT	Frequency	N	Mean	Median	Std. Deviation
Age	-	100	25.89	24.00	7.45
Years of Education	-	100	14.04	15.00	2,22
Body Mass Index	-	100	22.95	22.62	3.71
Gender					
male	50%	50	-	-	-
female	50%	50			
Civil Status					
single	86%				
married	9%				
divorced	1%	100	-	-	-
widow	1%				
living together	3%				
PCS					
Catastrophizing	-	30	1.67	1.62	0.66
Depression	-	66	4.09	3.00	3.16
HADS					
Anxiety	-	66	7.09	7.00	3.00
Total	-	66	11.18	9.50	5.90
Noticing	-	93	2.51	2.67	1.31
Not-distracting	-	92	1.21	1.00	0.95
Not-worrying	-	93	1.97	2.00	1.29
Attention regul.	-	92	2.14	2.53	1.37
MAIA					
Emotional awareness	-	92	2.65	3.10	1.51
Self-regulation	-	91	1.91	2.00	1.26
Trusting	-	91	2.90	3.33	1.36
Sum	-	52	5.44	2.91	13.67

Table 2 - N, Mean, Median and Standard Deviation of the Portuguese population

In the Portuguese sample, 50 subjects were male and 50 were female with mean and standard deviation of age: 25.89 ± 7.45 , ranging between 18 and 53 years old. Regarding the educational background, 3% of the subjects have the 9^o grade, 42% did

gain a high school education and 55% followed a higher education. The majority of them were single (86%) with a B.M.I. average and std. deviation of 22.95 ± 3.71 .

Individual differences were assessed in Portugal with the PCS, HADS, and MAIA. The total score of PCS had a mean of 1.67 ± 0.66 ; the HADS had a mean of 4.09 ± 3.16 for depression, 7.09 ± 3.00 for anxiety and 11.18 ± 5.90 as total; and finally, the MAIA 8 subscales had Noticing with a mean of 2.51 ± 1.31 ; Not-distracting with 1.21 ± 0.95 ; Not-worrying with 1.97 ± 1.29 ; Attention regulation with 2.14 ± 1.37 ; Emotional awareness with 2.65 ± 1.51 ; Self-regulation with 1.91 ± 1.26 ; Trusting with 2.90 ± 1.36 ; Sum with 5.44 ± 13.67 .

Table 3 - Demographic information and individual differences, measured by the questionnaires, from Israeli participants.

ISR		Frequency	N	Mean	Median	Std. Deviation
Age		-	352	24.65	23.00	5.08
Years of Education		-	346	14.54	15.00	1.81
Body Mass Index		-	281	23.26	22.60	3.89
Gender	male	43.5%	153			
	female	56.5%	199	-	-	-
Civil Status	single	86.6%				
	married	11.1%				
	divorced	0.9%	347	-	-	-
	widow	-				
	living together	-				
SCSR	internal attention	-	184	18.47	19.00	3.40
	external attention	-	184	12.89	13.00	3.20
	anxiety	-	184	7.73	8.00	3.70
PSQ	mild	-	250	4.43	4.29	1.70
	moderate	-	250	5.89	5.86	1.57
	total	-	250	5.47	5.57	1.58
LOT	optimism	-	251	19.58	20.00	4.74
	pessimism	-	251	7.45	7.00	3.19
	total	-	251	10.22	11.00	2.69
PCS	catastrophizing	-	184	21.58	20.00	11.88
	rum	-	184	7.59	8.00	4.81
	mag	-	184	4.79	5.00	2.97

help	-	184	9.20	9.00	5.59
BAQ	-	139	83.45	84.00	16.57

Table 3 - N, Mean, Median and Standard Deviation of Israel population

In the Israeli sample, 153 subjects were male and 199 were female with mean and standard deviation of age 24.65 ± 5.08 , ranging between 18 and 53 years old. Regarding the educational background, 21.6% of the subjects did have a high school education and 76.7% followed a high education (6 subjects had missing information). The majority of them were single (86.6%) with a B.M.I. average and std. deviation of 23.26 ± 3.89 .

The individual differences of the study participants were assessed in Israel using SCSR, PSQ, LOT, PCS, and BAQ. Starting with SCSR with 3 subscales: internal attention with a mean and std. deviation 18.47 ± 3.40 ; external attention with a mean of 12.89 ± 3.20 ; and anxiety with a mean of 7.73 ± 3.70 . The PSQ with 3 subscales: mild with a mean of 4.43 ± 1.70 , moderate with a mean of 5.89 ± 1.57 , and the total with a mean of 5.47 ± 1.58 . LOT also with 3 subscales with a mean of 19.58 ± 4.74 for optimism, 7.45 ± 3.19 for pessimism and 10.22 ± 2.69 as total; PCS with 4 subscales: catastrophizing with a mean of 21.58 ± 11.88 , rrum of 7.59 ± 4.81 , mag of 4.79 ± 2.97 and help with 9.20 ± 5.59 . Lastly, the BAQ scale with a mean of 83.45 ± 16.57 .

The normality of the demographic variables for each country was analyzed through the Shapiro-Wilk. Since all the sig. values of Shapiro-Wilk are $p < .05$, making them statistically significant it can be concluded that the null hypothesis, where there's no statistical relationship and significance exists in a set of given single observed variables, can be accepted, i.e. that the variables deviate from a normal distribution meaning that non-parametric test must be applied (see table 1 - Annex 1).

Further, performing the analysis, the variables: Age, Education, and BMI went through the Mann-Whitney test since they are Nominal; and the Gender and Civil Status through a chi-square test because it's a Scale. The Mann-Whitney test revealed that there are no significant differences between the variables Age (Mann-Whitney $U = 18279.00$, $\rho = .554$), Education (Mann-Whitney $U = 15222.50$, $\rho = .061$) and B.M.I. (Mann-Whitney $U = 13400.50$, $\rho = .492$) but there is a significant positive difference in Gender ($\chi^2 = 4.681$, $\rho = .030$) with $\rho < .05$, and also, the Civil Status ($\chi^2 = 1289.14$, $\rho = .001$) with $\rho < .01$, meaning that there are significantly more males in ISR than in PT, and the majority are single.

4.3 Individual differences comparison with Demographic and FAST outcomes

The normality of the individual variables for each country was analyzed through the Shapiro-Wilk. Since all the sig. values of Shapiro-Wilk are $\rho < .05$, making them statistically significant it can be concluded that the null hypothesis, where there's no statistical relationship and significance exists in a set of given single observed variables, can be accepted, i.e. that the variables deviate from a normal distribution meaning that non-parametric test must be applied.

Regarding the individual variables of the scales applied, the only one that can be compared between both samples (PT and ISR) through the Spearman-rho test is PCS catastrophizing. The results indicate a negative correlation between the variable and the two groups ($r_s = -.588$; $\rho = .001$), meaning that Israel has significantly higher amounts of pain catastrophizing than Portugal.

Also, a correlation between the FAST outcomes and the clinical variables, specifically, the PCS catastrophizing, HADS and MAIA from PT and ISR was performed using the Spearman test. The results concluded that there is no significant correlation between both in PT. Nevertheless, in ISR there's correlations between ICC and PSQ total ($r_s = .168$; $\rho = .008$), R^2 linear and LOTtotal ($r_s = -.219$; $\rho = .001$), ICC and LOTr pessimism ($r_s = .385$; $\rho = .001$), and lastly, R^2 linear and LOTr optimism ($r_s = .197$; $\rho = .002$).

Additionally, there's no significant correlation between the demographic variables and any of the individual variables evaluated through the scales and questionnaires.

4.4 Experimental Pain Variability - FAST outcome measures

This analysis was based on a comparison between the descriptive statistics of three main FAST results: R², ICC, and CoV, and the demographic variables (PT vs ISR).

Table 4 - Characterization of the FAST variables in each sample.

		N	Mean	Median	Std. deviation	P-value^a
Portugal	R² linear	95	0.51	0.53	0.15	.001
	ICC	96	0.60	0.61	0.17	.001
	Cov	96	0.56	0.44	0.37	.001
Israel	R² linear	346	0.59	0.61	0.14	.001
	ICC	346	0.73	0.75	0.17	.001
	CoV	282	0.80	0.77	0.39	.001

Table 4- Descriptive statistics of FAST between Pt and Isr

^a Mann-Whitney test. This is a lower bound of the true significance.

In Portugal the mean of R² linear is M = 0.51 (DP = 0.15), the ICC is M = 0.60 (DP = 0.17) whereas of CoV is M = 0.56 (DP = 0.37). And in Israel the mean of R² linear is 0.59 (DP = 0.14), of R² Power is M = 0.48 (DP = 0.15), of ICC is M = 0.73 (DP = 0.17), furthermore of CoV is M = 0.80 (DP = 0.39).

The normality of the FAST was analysed through the Shapiro-Wilk. The sig. values of Shapiro-Wilk are all $\rho < .05$, making them statistically significant so it can be concluded that the null hypothesis, can be accepted, i.e. that the variables deviate from a normal distribution (see table 2 - Annex 1).

Therefore, for the comparative analysis the non-parametric Mann-Whitney test was applied. The Mann-Whitney test revealed that there is a significant difference, between groups (PT and ISR) in the 3 FAST outcomes: R² linear (Mann-Whitney $U = 11383.50$, $\rho = .001$), ICC (Mann-Whitney $U = 9573.50$, $\rho = .001$), and CoV (Mann-Whitney $U = 8460.00$, $\rho < .001$) with $\rho < .01$ meaning that the outcomes in ISR are higher than in PT, i.e. there is more variability in answers for R² and ICC. On the other side, there is less variability in ISR than in PT for CoV, i.e., more precision in the answers.

4.5 Short-term memory - Digit Span outcomes measures

In terms of the short-term memory measured by the Digit Span Scale the N, means, median, std deviation between both samples were analyzed.

Table 5 - Characterization of the Digit Span variables in PT and ISR.

		N	Mean	Median	Std. Deviation	p-value^a
Portugal	Digit Span	24	6.79	6.00	1.41	.001
	Digit Span Reverse	24	5.66	5.50	1.21	.389
	Digit Span Total	29	12.24	12.00	2.34	.001
Israel	Digit Span	123	9.56	10.00	1.86	.001
	Digit Span Reverse	123	5.26	5.00	2.06	.389
	Digit Span Total	123	14.82	14.00	3.20	.001

Table 5 - N, Mean, Median and Standard Deviation of General Population

^a Mann Whitney test.

For Portugal, the mean for the Digit Span variable is 6.79 ± 1.41 ; for Digit Span in Reverse the mean is 5.63 ± 1.21 and for the total of Digit Span it is 12.24 ± 2.34 . For Israel the media for the Digit Span variable is 9.56 ± 1.81 ; for Digit Span Reverse the mean is 5.26 ± 2.06 and for the total of Digit Span it is 14.82 ± 3.20 .

The normality of the Digit Span was analyzed through the Shapiro-Wilk. The Digit Span Reverse ($\rho = .099$) and Digit Span Total ($\rho = .341$) in Portugal are $\rho > .05$ meaning that they aren't statistically significant and it can be concluded that the null-hypothesis, can be rejected, i.e. these two follow a normal distribution across the locations. The remain aren't normally distributed (see Table 3 - Annex 1).

Since the majority of the samples don't follow a normal distribution, to do a comparative analyse a non-parametric test, Mann-Whitney test, was applied. The test revealed that there is a significant difference, in Digit Span (Mann-Whitney $U = 366.00$, $\rho = .001$) and Digit Span Total (Mann-Whitney $U = 919.50$, $\rho = .001$) with $\rho < .01$, this means that the score in ISR is significantly higher than PT, i.e. ISR has better short-term memory than PT. The Digit Span in Reverse (Mann-Whitney $U = 1635.00$, $\rho = .398$) revealed no significant differences.

4.6 Correlations between demographic differences and FAST

A bivariate correlation between the three FAST outcomes and the five demographic variables from PT and ISR was performed by using the Spearman-rho results.

Table 6 - Correlation between FAST and demographic variables.

			Age	Gender	Years of Education	Civil Status	BMI
Portugal	R ² linear	C.C.	-.168	-.217*	.001	-.169	-.059
		Sig.	.104	.035	.997	.102	.570
	ICC	C.C.	-.073	-.288**	.101	-.139	-.038
		Sig.	.478	.004	.326	.178	.716
	CoV	C.C.	-.026	-.291**	.045	-.218*	-.070
		Sig.	.085	.004	.665	.033	.501
Israel	R ² linear	C.C.	.093	-.038	-.064	.065	-.028
		Sig.	.085	.484	.237	.233	.641
	ICC	C.C.	.100	.003	.063	.066	.032
		Sig.	.062	.960	.245	.226	.596
	CoV	C.C.	.076	.035	.044	.034	-.042
		Sig.	.205	.559	.464	.572	.483

Table 6 - *. Correlation is significant at the 0.01 level (2-tailed).

** . Correlation is significant at the 0.05 level (2-tailed).

Analysing the PT results there is a significant correlation between R² linear and the Gender ($r_s = -.217$; $\rho = -.035$), ICC and the Gender ($r_s = -.288$; $\rho = -.004$), CoV and the Gender ($r_s = -.291$; $\rho = -.004$), all meaning that a lower variability is related to the male gender, and also, CoV and the Civil Status ($r_s = -.218$; $\rho = -.033$), meaning single people are worse at reporting pain, with $\rho < .05$. There aren't any significant differences between the other variables. In ISR, performing the comparative analysis, no significant differences were found between any variable.

4.7 Correlations between variability in pain reports and short-term memory

Since there's no normality among most variables the statistical analysis of the Digit Span vs Fast was performed through a bivariate correlation between both using the Spearman test.

Table 7 - Correlation between FAST and the Digit Span.

			R² linear	R² power	ICC	CoV
Portugal	Digit	r_s	-.500*	-	.065	-.139
	Span D.	Sig.	.018	-	.233	.526
	Digit	r_s	-.394	-	-.015	-.176
	Span	Sig.	.069	-	.806	.423
	Reverse	r_s	-.239	-	.066	.067
	Span	Sig.	.230	-	.226	.737
	Total					
Israel	Digit	r_s	.131	.037	-.073	.031
	Span D.	Sig.	.149	.726	.426	.722
	Digit	r_s	.126	.061	.260**	.243*
	Span	Sig.	.166	.560	.004	.019
	Reverse	r_s	.183*	.094	.158	.172
	Span	Sig.	.043	.366	.083	.099
	Total					

Table 6 *. Correlation is significant at the 0.01 level (2-tailed).

***. Correlation is significant at the 0.05 level (2-tailed).

Analyzing the results there is a significant correlation between R² linear and the Digit Span direct in PT ($r_s = -.500$; $\rho = .018$). This means that a worse performance on the more attention-related task is associated with less variability, or better ability to accurately assess pain stimuli presented. However, R² linear and the Digit Span Total in ISR ($r_s = .183$; $\rho = .043$) are correlated in the opposite direction, which means that the short-term memory task is related to greater precision in the assessment of experienced pain (less variability), and CoV with Digit Span Reverse in ISR ($r_s = .243$; $\rho = .019$), meaning that the performance on the working memory task is associated with less consistency in the assessment of experienced pain, all $\rho < .05$. There's also a statistically significant difference between ICC and Digit Span Reverse in ISR ($r_s = .260$; $\rho = .004$)

which is $\rho < .01$ and means that better performance on the working memory task is associated with greater reliability in the assessment of experienced pain. There are not any significant differences between the other samples.

5. Discussion

The current study aimed to explore the relationship between experimental pain variability, measured with FAST and demographic characteristics (such as age, gender, education, civil status, B.M.I), individual differences (measured by questionnaires applied), and short-memory (measured with Digit Span), in the two populations, from PT and ISR. It was found that there are differences in the within-subject variability of pain intensity reports between the two cohorts: The ISR participants demonstrated lower variability compared to Portuguese. It was also found there might be differences in the ability to assess pain between genders and civil status. About the individual characteristics there is a significant relation between the PCS catastrophizing between both countries meaning that ISR is better a catastrophising pain. Moreover, significant correlations were found between the results of the short-term memory task and the within-subject variability.

The multiplicity of painful experiences, the uniqueness of pain challenges the ability to evaluate this experience. The perception, response, evaluation, and treatment of pain are modified by numerous factors that influence people's experience of pain, such as the gender (Ostrom et al, 2017) and catastrophizing pain (Sullivan, 1995) yet is still limited knowledge regarding factors that might influence the task of mentally infer the magnitude of the stimuli felt (the within-subject variability). For this reason, studies assessing the importance of demographic, individual, and/or clinical evaluations are important to better understanding and overall treat pain-related diseases The current study aimed to shed light on some of these potential factors.

5.1 Relation between location and FAST outcomes

The first objective was to compare the differences in pain variability and its correlations in two different cultural groups (Portugal and Israel). This was mainly done to understand the potential impact of cultural influences in pain reporting. Significant differences were found in the 3 FAST outcomes between ISR and PT, meaning that the results Israelis demonstrate lower within-subject variability in their pain intensity reports in response to experimental pain stimuli than the Portuguese. Studies analyzing the impact of culture have been mostly dedicated to studying differences in pain perception and not differences in the pain reporting variability. Greenspan et al., 2007 supposed that gender-specific pain perception patterns differ between cultures, indicating sociocultural

origins or maybe racial inequities may importantly impact how pain is felt and/or perceived. Similarities and disparities across cultures reflect biological or biopsychological mechanisms. The study already mentioned by Miller and her colleagues in 2020, that found that Black patients rated as more distressed and were more interfered by their pain than White patients indicates that there may also be cultural differences in the ability to report. A possible explanation may be a greater familiarity with the use of pain assessment scales. Relating with PT and ISR, in PT, only in recent years have been noticed a greater frequency of use of pain assessment scales (and even other dimensions), maybe our health model until now was very centred on the authority of health professionals and less on the patient health perspective.

It should be mentioned, however, that it cannot be ruled out that the differences between the two groups might be a consequence of differences in the details during the application of the tools and instruments between the two laboratories. Despite the use of the same protocols, instructions, and guidelines, small differences might have an impact on the results found.

5.2 Relation between demographic variables and FAST outcomes

The second goal of this study was to explore if demographic differences such as age, gender, years of education, civil status, or BMI are related to the experimental variability of pain (measured by FAST outcomes). Correlations were found between Gender and the FAST in PT and, contrarily, no association between the demographic variables and the FAST in ISR. Analysing in detail the PT results there is an association between R^2 linear ($r_s = -0.217$; $\rho = -.035$), ICC ($r_s = -0.288$; $\rho = -.004$), and CoV ($r_s = -0.291$; $\rho = -.004$) with the Gender variable with $\rho < 0.05$, meaning that a better capacity to report pain (less variability) is related to the male gender. A few studies suggest that women, in comparison to men, experience a disproportionately higher number of pain disorders and dominate those pain disorders by a considerable margin resulting in possibly higher pain sensitivity (Ostrom et al, 2017). However, to our knowledge, there are no current studies studying gender differences in the within-subject pain variability. The direction of results that suggest that women experience higher variability may be aligned with literature on pain sensitivity and modulation. Since females are more vulnerable to pain, and experience more pain in their lives, they may be more affected by more biological, emotional, and contextual events thus resulting in more inconsistent pain reporting (Lumley et al., 2011).

These results about gender differences were not found in the two countries. This discrepancy deserves further clarification and further comprehensive studies between men vs women in pain reports.

Another relevant result was the differences in the Civil Status ($r_s = -.218$; $\rho = -.033$) with $\rho < 0.05$, meaning that single people are better at reporting pain. This may be explained since the majority of the sample (86%) is single in the PT sample and the heterogeneity of the sample in this precise aspect may have influenced the results. There aren't any significant differences between the other variables.

5.3 Relation between individual differences and FAST outcomes

For the third objective, to explore the relations between clinical characteristics (measured by questionnaires) and the variability of pain (measured by FAST outcomes), The comparison between individual differences measured by the questionnaires between the two countries was only possible in $N=30$ and specifically for the catastrophizing PCS scale. There was a negative association $r_s = -.588$; $\rho = .001$ between the 2. Israel has significantly higher scores than Portugal. As stated before, the PCS catastrophizing scale is a self-report measure designed to assess catastrophic thinking related to pain among adults with or without chronic pain (Sullivan, 1995). Cultural differences between both countries may explain these results, but as far as we know there are no current studies on cultural differences in catastrophization.

The analysis of the results of each country indicated that there is no correlation between FAST results in Portugal and the individual differences measured (PCS catastrophizing, HADS, and MAIA). This lack of correlations can have two interpretations: one is that the individual characteristics measures are not indeed related to variability in pain reports. Previous studies on FAST fail to find correlations with the general clinical questionnaires used, even in clinical populations (Treister, Eaton, Trudeau, Elder & P Katz, 2017) (Khallouf, 2019). This might indicate that these characteristics are not relevant to the variability of pain reports. Another reason may be more related to methodological issues: the heterogeneity in the number of participants and studies in which the questionnaire data was collected was highly variable.

Similar interpretations can be done for the Israel participants. However, in this it was found a significant correlation between ICC and PSQ total ($r_s = .168$; $\rho = .008$). Meaning that less stress means better capacity to report pain.

Lastly, there's correlations between ICC and LOTr pessimism ($r_s = .385$; $\rho = .001$), R² linear and LOTr optimism ($r_s = .197$; $\rho = .002$) and between R² linear and LOTtotal ($r_s = -.219$; $\rho = .001$). being inconsistent and conflicting relations the reason for the occurrence are not well known. This suggests that an optimistic mindset is related to a better report pain capacity, i.e. higher stress suggests worst precision in pain report. In many aspects, sensibility to pain and stress are connected so, maybe the variability is also connected to stress (Chen et al., 2021). A study conducted by Buchanan & Seligman, in 1995, stated that individuals with high levels on measures of dispositional optimism report fewer depressive symptoms, excellent use of coping strategies, and fewer physical symptoms when compared to pessimistic individuals. Optimism is also associated with high levels of motivation and physical well-being, as well as low levels of symptoms depressives. So, there's a need for further studies and also reapplying these two specifically scales in similar samples.

5.4 Relation between Digit Span outcomes and FAST outcomes

The last objective of this study was to explore the correlations between short-term memory (measured by the Digit Span Task) to the variability of pain reports (measured by FAST outcomes). In other words, the aim was to explore if there was an association between participants with better responses on Digit Span and those with lower within-subject pain reporting on FAST or not. Starting with the PT sample, there is a negative correlation between R² linear and the Digit Span direct in PT ($r_s = -.500$; $\rho = .018$), which means that the participants were less accurate at rating pain tended to be worse at the attention/working memory capacity.

Short-term memory was assessed in these studies of experimental pain variability because it is believed that during the FAST procedure, a requirement to assess each stimulus, is to mentally compare its intensity with the stimulus presented a few seconds ago. This may require good short-term abilities. In this view, it would be expected that short-term memory was correlated to FAST performance, i.e., higher precision in pain rating (less variability, higher results on R² and ICC, and lower in CoV). The results gathered were unexpected, since in the Portuguese sample they were in the opposite direction, making them hard to interpretate.

On the other side, in the Israel studies, the expected correlations were found: There was a significant positive correlation between the three FAST outcomes and Digit Span Reverse and Digit Span Total. Specifically, CoV with Digit Span Reverse in ISR ($r_s =$

.243; $\rho = .019$). This means that the performance on the working memory task is associated with less consistency in the assessment of experienced pain, ICC and Digit Span Reverse in ISR ($r_s = .260$; $\rho = .004$), meaning that the performance on the working memory task is associated to greater reliability in the assessment of experienced pain. Lastly, R^2 linear and the Digit Span Total ($r_s = .183$; $\rho = .043$) mean that the short-term memory task is related to greater precision in the assessment of experienced pain (less variability). As it's known, Reverse digit memory requires greater effort from working memory (Wechsler, 2008) and all the results go accordingly to the hypothesis that better working memory individuals give more accurate pain reports.

6. Limitations

Given the results found, one of the major limitations is undoubtedly that the sample collection was carried out in different laboratories. As a consequence, differences between procedures, study protocols, and data collection may explain the differences found. Even though there are strict and written guidelines concerning the application of FAST it cannot be excluded the possibility of bias or other differences that could impact the study results. The same could have occurred in the cognitive task used.

Still, within the same umbrella, all the data included were obtained from several studies, and these would have different objectives and hypotheses, possibly directing a greater relevance to certain procedures than to others.

These two limitations contributed to the heterogeneity of the sample, leading to large discrepancies in comparisons between demographic variables such as the gender gap between men and women in Israel; the clinical variables being only possible to compare 30 individuals in the two populations concerned of the scale of PCS catastrophizing out of the total of 452 participants; and Digit Span with a maximum of 123 participants from Israel, being an even smaller number in Portugal.

All these discrepancies collaborated in the constitution of a heterogeneous sample, possibly reflected in the results and conclusions derived from the study. To get around this limitation, I propose a reapplication both in Portugal and in Israel following a universal protocol, properly descriptive and detailed, to avoid missing values or discrepancy in the sample and take special care with clinical variables. Also, the study should not be limited to Portugal and Israel, but rather be extended to other countries and different cultures in the world to have a better concept of the pain and impact that demographic variables have on it. Lastly, a new study with equal and bigger samples to study the most promising variables found in this study. To do so the following questionnaires and scales could be used to assess clinical distress: SCS-R, PSQ, LOT, HADS, but also, Brief Pain Inventory (BPI), already addressed in this study, and lastly the Multidimensional Personality Questionnaire–Simplified-Wording Form (MPQ-SF) that is an instrument to do personality assessment informing lower- and higher-order personality dimensions. Regarding memory assessment, an evaluation of the level of pre-morbid intelligence of the participants is having a control measure. Ideally, training should be applied together, mainly from FAST, so that each individual was prepared and familiarized with the protocol. Finally, regarding the influence of the memory in pain

variability, in the studies previously mentioned can have another form of painful stimuli and another memory tasks such as the Wechsler Memory Scale (WMS) that is designed to measure different memory functions in a person. A person's performance is reported as five Index Scores: Auditory Memory, Visual Memory, Visual Working Memory, Immediate Memory, and Delayed Memory to see if there is any area that impacts more in pain variability (Loring, 1989).

7. Final Conclusions

Pain is an important function to alert the body to potential damage so it is vital a good pain assessment to understand variability of pain to treat. This study explored some characteristics in healthy population that may influence pain sensitivity, in an attempt to obtain some clues about variables that influence pain variability. It concluded that gender, stress, optimism and short-term memory have potential and need to be better explored in future studies. Along with, cultural differences may also affect pain sensitivity.

However, the FAST vs Digit Span results, especially from the Israel sample, revealed that short-term memory skills may be important for reducing variability in pain ratings and potential people to be more accurate. This finding could have clinical implications, indicating the need for further research into how cognitive performance in general links to the ability to report pain and other symptoms. These results also meet the earlier studies that show the role of expectations in pain variability (Treister et al., 2019).

It is necessary to increase the number of studies concerning within-subject pain variability to better understand its processes. This might contribute to increasing and improving therapeutical options to reduce pain, a worldwide problem with a huge impact on the economical, personal, and social life of millions of individuals.

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9. Annex

Annex 1:

Table 1 - Normality Analysis of the Demographic Variables.

		Shapiro-Wilk	Skewness	Kurtosis	p-value
Age	Portugal	.001	1.73 ± 0.24	2.99 ± 0.48	.554 ^a
	Israel	.001	2.07 ± 0.15	5.65 ± 0.30	
Gender	Portugal	.001	0.00 ± 0.24	-2.04 ± 0.48	.030 ^{b*}
	Israel	.001	-0.22 ± 0.15	-1.97 ± 0.30	
Education	Portugal	.001	-0.09 ± 0.24	-1.11 ± 0.48	.061 ^a
	Israel	.001	0.29 ± 0.15	-0.22 ± 0.30	
Civil Status	Portugal	.001	3.73 ± 0.24	14.15 ± 0.48	.001 ^{b*}
	Israel	.001	2.68 ± 0.15	6.84 ± 0.30	
BMI	Portugal	.001	0.72 ± 0.24	0.51 ± 0.48	.492 ^a
	Israel	.002	1.11 ± 0.15	1.99 ± 0.30	

Table 1 - ^{a)} 2 independent samples - Mann-Whitney test; ^{b)} chi-square test.

Table 2 - Normality Analysis of the FAST Variables.

		Shapiro-Wilk	Skewness	Kurtosis	p-value^a
R² linear	Portugal	.001	-0.65 ± 0.25	0.43 ± 0.49	.001
	Israel	.025	-1.12 ± 0.15	1.98 ± 0.29	
R² power	Portugal	-	-	-	-
	Israel	.008	-0.41 ± 0.16	-0.12 ± 0.32	
ICC	Portugal	.042	-4.94 ± 0.25	-1.11 ± 0.49	.001
	Israel	.001	-1.44 ± 0.15	2.79 ± 0.29	
CoV	Portugal	.001	0.99 ± 0.25	0.22 ± 0.49	.001
	Israel	.001	0.33 ± 0.15	-0.50 ± 0.29	

Table 2 - ^a Mann Whitney test. This is a lower bound of the true significance.

Table 3 - Normality Analysis of the Digit Span Variables

		Shapiro-Wilk	Skewness	Kurtosis	p-value^a
Digit Span	Portugal	.002	0.40 ± 0.47	-0.622 ± 0.92	.001
	Israel	.001	0.49 ± 0.22	0.079 ± 0.43	
Digit Span Reverse	Portugal	.099	0.16 ± 0.47	0.192 ± 0.92	.398
	Israel	.002	0.05 ± 0.22	-0.561 ± 0.43	
Digit Span Total	Portugal	.341	0.28 ± 0.47	-0.403 ± 0.92	.001
	Israel	.007	0.46 ± 0.22	0.023 ± 0.43	

Table 3 - ^a Mann Whitney test. This is a lower bound of the true significance.