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Modulation of Nociception and Pain by Attention and Stress

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Résumé

Les facteurs psychologiques tels que l'hypnose, l'émotion, le stress et l'attention exercent un effet modulant puissant sur la nociception et la douleur. Toutefois, l'influence de l'attention sur la nociception et la douleur, ainsi que les mécanismes neuronaux sous-jacents, ne sont pas clairs. La littérature actuelle sur la modulation attentionnelle des réponses spinales nociceptives, telles que mesurées par le réflexe RIII, et de la perception de l'intensité de la douleur est discordante et souvent contradictoire. Ce mémoire fournit un nouveau cadre pour examiner la modulation du réflexe RIII et de la douleur par l'attention. Une tâche de discrimination sensorielle a été décomposée en trois composantes attentionnelles : la vigilance, l'orientation, et le contrôle exécutif. Auparavant, la nature multidimensionnelle de l'attention fut largement ignorée dans la littérature. Nous démontrons que les composantes attentionnelles ont des effets modulatoires distincts sur la nociception et la douleur et suggérons que ceci représente une partie de la confusion présente dans la littérature. En prenant compte du stress indépendamment, nous démontrons, pour la première fois, que le stress inhibe la modulation attentionnelle du réflexe RIII ce qui indique une interaction et dissociation de la modulation des réponses nociceptives par l'attention et le stress. Ces résultats importants clarifient, en grande partie, les contradictions dans la littérature, puisque les tâches cognitives produisent souvent des augmentations du stress ce qui confond l'interprétation des résultats. De plus, la tâche de discrimination inclut des stimuli visuels et somatosensoriels et révèle que l'influence de l'attention sur la douleur est spatialement spécifique tandis que la modulation attentionnelle de la nociception est spécifique à la modalité des stimuli, au moins en ce qui concerne les modalités examinées. A partir de ces résultats, un nouveau modèle de la modulation attentionnelle des processus de la douleur, basée sur les composantes attentionnelles, a été

proposé. Celui-ci est appuyé par la littérature et fournit une explication systématique et intégratrice des résultats antérieurement contradictoires. De plus, à partir de ce modèle, plusieurs mécanismes neuronaux ont été proposés pour sous-tendre la modulation attentionnelle de la nociception et de la douleur.

Mots clés : Douleur, nociception, réflexe RIII, attention, stress, modulation de la douleur, composants attentionnels.

Abstract

Psychological factors such as hypnosis, emotion, stress, and attention produce powerful modulatory effects on nociception and pain. However, the influence of attention on nociception and pain and the underlying neural mechanism responsible are unclear. The current literature on attentional modulation of spinal nociceptive responses, as measured by the RIII reflex, and pain perception (pain intensity) is inconsistent and often contradictory. The present thesis provides a new component-based framework for the examination of attentional modulation of the RIII reflex and pain. A delayed-discrimination task was decomposed into the three components of attention – namely alerting, orienting, and executive control (sensory working memory). Previously, the multidimensional nature of attention was largely ignored in the pain literature. We show that each component of attention exerts a distinct modulatory effect on nociception and pain and suggest that this accounts for some of the confusion in the literature. By considering stress separately, we demonstrate for the first time that stress blocks attentional modulation of the RIII reflex, indicating an interaction and dissociation of attention- and stress-mediated modulation of spinal nociceptive responses. This important finding clarifies much of the disagreement in the literature, since cognitive tasks often induce increases in stress that consequently confound interpretation. Additionally, both visual and somatosensory stimuli were included in the discrimination task, revealing that the influence of attention on pain intensity is spatially-specific whereas attentional modulation of nociception is modality-specific, at least for the modalities investigated. From these findings a component-based model for the attentional modulation of pain processes is proposed. This model is substantially supported by the literature and provides a meaningful and cohesive

explanation of the seemingly contradictory results across studies. Moreover, this model suggests potential neural mechanisms underlying the attentional modulation of pain.

Keywords : Pain, nociception, RIII reflex, attention, stress, pain modulation, attentional components.

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ACC – anterior cingulate cortex

ANT – attention network test

BOLD – blood oxygenation level dependent

BP – blood pressure

CIP - congenital insensitivity to pain

ECG – electrocardiogram

EEG – electroencephalogram

fMRI – functional magnetic resonance imaging

GSR – galvonic skin response

HR – heart rate

INS – insula

LC – locus coeruleus

NE – norepinephrine

NFR - Nociceptive Flexion Reflex

NRS – numerical rating scale

PAG- periaqueductal grey matter

PASAT – paced auditory serial addition task

PET – positron emission tomography

PFC – prefrontal cortex

PMR – progressive muscle relaxation

RR – respiration rate

RT – reaction time

S1 – primary somatosensory cortex

S2 – secondary somatosensory cortex

SCR – skin conductance response

SIA – stress-induced analgesia

THAL – Thalamus

TSST – Trier social stress test

VAS – visual analogue scale

VLM – ventrolateral reticular formation

VRS – verbal rating scale

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Chapter 1: General Introduction

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"The greatest evil is physical pain." (Saint Augustine (354-430).

Pain is the number one reason that North Americans seek medical attention (Statistics Canada, 2010). Although our current understanding of pain has long surpassed our predecessors' theories that these sensations emanate from evil, the appeal for a more thorough understanding of the peripheral and central neural mechanisms underlying pain and the factors that influence these mechanisms is ever present and remains highly relevant.

Pain is a complex sensory and affective experience that acts as the body's alarm to present and potential physical harm. Nociception is the processing of information by the peripheral and central nervous system elicited by the activation of nociceptors, whereas pain is a multidimensional experience involving higher order processing that underlies the subjective sensation. Nociception and pain are of great physiological importance and are thought to have evolved to provide organisms with a system that alerts them to potential physical threat and produce protective withdrawal and aversion responses (Perl, 2011). The multidimensional nature of pain (with its auto-defensive qualities) distinguishes it from the other senses, such as vision, touch, smell, sound, and taste, and imparts it with a unique and distinctive nature. Although a deficit in one of the other sensory systems can lead to numerous obstacles and difficulties, individuals lacking the ability to perceive pain, such as those suffering from congenital insensitivity to pain (CIP), experience significantly higher incidence of injury and untreated illness and lower life expectancy (Nagasako et al., 2003), highlighting the biological importance of such a system. Despite its protective role, under certain circumstances pain can

become maladaptive as a result of changes in normal pain processing, and can lead to chronic pain conditions (Perl, 2011). Developing better treatment options for acute and chronic pain remains a prominent goal in clinical research and fuels the need for further advances in fundamental research on pain.

Pain is a composite of multiple components and is influenced by a wide range of elements – physiological, pharmacological, and psychological/cognitive factors affect pain processing and perception (Price et al., 2004). It is this complex multi-faceted nature of the pain experience that simultaneously incites further examination and challenges our ability to do so. To date, much interest has been focused on pharmacological modulation of pain in an attempt to address the clinical need for pain relief. As polypharma is becoming an ever-growing problem, some attention has been redirected to psychological and cognitive factors that influence pain processing. Previous research has demonstrated that pain perception is influenced by higher order processes such as emotion, expectation, and attention. The ability to modulate pain by cognitive factors such as attention is an area of current interest and remains to be thoroughly explored and understood.

The main focus of this work is to examine the influence of higher order processes, specifically attention and stress, on nociception and pain. In order to undertake this feat, the current state of the field is first assessed by analyzing what is presently known about these processes, what remains to be determined, and the tools available for investigation in this area of study. To this end, an overview of pain transmission from receptor to cortex will be presented, followed by an overview of factors currently recognized to modulate pain, and finally a description of the Nociceptive Flexion Reflex (NFR), also known as the RIII reflex, as an objective measure of spinal nociceptive transmission. With this foundation in place, the

current literature on the modulation of the NFR and pain by attention will be described, highlighting the gaps in our current understanding. Hypotheses were developed based on the current literature and form the basis that direct the research presented in this thesis.

1.1 From Toe to Head: What is pain and how does it work?

Humankind has long sought to understand the origins and nature of pain. Prior to our familiarization with the human nervous system, some of the earliest beliefs about pain emphasized spiritual and theological sources. Pain was believed to result from bodily intrusions of evil spirits, which were thought to be remedied by spiritual incantations and prayer, or it was assumed to represent an imbalance of "vital fluids" remedied by treatments such as bloodletting. With the practice of dissecting human cadavers and the exploration of human anatomy came a shift towards an empirical approach to the investigation of pain. The publication of Rene Descartes' philosophy of the body as a machine, with its famous drawing of a pain pathway depicting a nerve fiber travelling through the body from the site of disturbance to the brain, marked a change from a mystical to a more scientific theory of pain. Aristotle and Plato regarded pain as an emotion; Descartes described it as a mechanical sensation.

Today, the International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". Thus, pain must be described as both a "mechanical sensory" and "emotional" experience. The sensory-discriminative component can be paralleled with neural processing present in other sensory systems and is made up of spatial and temporal aspects, as well as the quality and intensity of the sensation. The motivational-

affective dimension of pain can be described as the emotional response that accompanies the sensory experience. A third dimension of pain, the cognitive-evaluative aspect, pertains to how pain perception is modulated by the cognitive appraisal of the sensory and affective experience. Together, these three dimensions of pain perception act in concert to produce the pain experience.

1.1.1 Neurobiology of Pain:

The pain experience typically begins with stimulation of nociception-specific receptors (nociceptors), which initiates a signal transduction cascade that ultimately leads to activation of supraspinal structures (Kandel et al., 2012). In contrast to the composition of other receptors of the somatosensory system, nociceptors are the free nerve endings of Aδ and C fibers, which are characterized by the nature of the stimuli that preferentially triggers a response: mechanical nociceptors are triggered by intense pressure; thermal nociceptors respond to temperatures above 45^{o}C and below 5^{o}C; polymodal nociceptors are stimulated by the former as well as by chemical agents; and finally, silent nociceptors are visceral afferents activated only following sensitization, such as in the presence of inflammation or specific chemical agents. The nociceptive signal initiated by stimulation of nociceptors is transmitted via Aδ and C fibers, which synapse in specific laminae of the dorsal horn of the spinal cord. Projection neurons in the spinal cord relay this information, directly or indirectly, via six main ascending pathways (spinothalamic tract, spinoreticular tract, spinomecenphalic tract, cervicothalamic tract, spinohypothalamic tract, and, spinocervical tract) to supraspinal structures involved in pain processing and perception, including thalamus (THAL), primary (S1) and secondary somatosensory cortices (S2), insula (INS), anterior cingulate cortex

(ACC), and prefrontal cortex (PFC). This nociceptive information, derived from the activation of nociceptors and the subsequent processing of this activity by the peripheral and central nervous system, is the foundation of the multidimensional pain experience. Nociceptive signals transmitted via these ascending pathways relay information that is integrated, along with other pertinent information, at the supraspinal level to then produce the multifaceted experience of pain.

The conceptual model of pain as a multidimensional construct is not purely philosophical; the sensory-discriminative, affective-motivational, and cognitive-evaluative components of pain are represented at the neural level. Mapping and neuroimaging techniques have given rise to the identification of brain areas involved in pain processing and perception. Brain regions that have been reported most often as involved in the pain experience, as evidenced by increased blood-oxygenation-level-dependent (BOLD) response, include S1, S2, THAL, ACC, INS and dorsolateral PFC (Apkarian et al., 2005). These same areas have also been identified by mapping studies in non-human primates as termination sites of nociceptive tracts (Dum et al., 2009). These regions, which are typically activated during the application of a painful stimulus, are not exclusively involved in pain processing. The non-pain-related functions of these structures provide insight and support to their hypothesized roles in pain processing. As a well established principle of neural functioning, S1, S2, and THAL have been shown to be directly involved in the perception of the spatial, temporal, and qualitative nature of innocuous stimulus intensity as a fundamental function in the somatosensory system. Not surprisingly, S1, S2, and THAL are generally considered to be primarily implicated in the sensory-discriminative aspect of pain. Functional magnetic-resonance-imaging (fMRI) studies have revealed that increased activation in these brain structures positively correlates with pain

intensity ratings of participants during application of painful stimuli, demonstrating their involvement in the sensory aspect of pain processing (Hofbauer et al., 2001; Coghill et al., 2013). Similar parallels can be found between the functions supported by other brain structures involved in pain processing and their role in the context of pain processing. Attention, motivation, error detection, and emotion are widely accepted as functional roles of the ACC as evidenced by numerous fMRI studies(Davis et al., 1997; Kandel et al., 2012). Functions of the INS include but are not limited to emotion, interoception, and autonomic regulation. In line with this, positive correlations have been found between pain unpleasantness ratings and the BOLD response to noxious stimuli in the ACC and INS, supporting their involvement in the affective-motivational dimension of pain (Rainville et al., 1999). Finally, the dorsolateral PFC is commonly associated with higher order functions including learning, memory, attention, and decision-making and is considered to be responsible for the cognitive-evaluative dimension of pain processing.

This general construct of a pain processing system that is composed of brain structures involved primarily in a particular dimension of pain is further supported by recent fMRI studies. Studies on hypnosis have found that selectively modulating either pain unpleasantness or pain intensity result in positively correlated changes in BOLD response in the dorsal ACC and S1, respectively, demonstrating a functional dissociation of these components of pain processing(Rainville, 1997; Rainville et al., 1999). The neural processing of pain can therefore be seen as a complex multidimensional system that involves a matrix of brain structures and peripheral pathways that integrates sensory-discriminative, motivational-affective and cognitive-evaluative components to produce the experience we call pain.

1.2 Toolbox for Studying Pain: *The Visual Analogue Scale and Nociceptive Flexion Reflex*

Our understanding of the neural mechanisms underlying the pain experience has been greatly advanced by the advent of methods that allow for the study of pain processing at various levels of the nervous system. The sensation of pain is most commonly associated with in changes in autonomic, spinal, and supraspinal activity, and therefore techniques to specifically measure each of these are of fundamental importance in order to advance our understanding of pain as a whole. Of the presently available methods, those most often employed in current research on pain include, but are not restricted to, galvanic skin response (GSR), heart rate (HR), electrocardiogram (ECG), respiratory rate, blood pressure (BP), NFR, subjective pain ratings, electroencephalogram (EEG), positron emission tomography (PET) and fMRI. Despite the inherent limitations of each method, together these tools provide critical information on how pain affects the nervous system and provides vital insight into what is happening at the autonomic, spinal, and supraspinal levels.

1.2.1 Supraspinal

In order to study what is going on at the supraspinal level we cannot simply open a person's head and examine the inner workings of the brain. To circumvent this obstacle, well established methods are available that provide measures of neural activity and subjective experience. The most widely used technique in current neuroscience research is BOLD fMRI, which takes advantage of predictable changes in blood oxygenation levels related to neural activity. From this relationship, a functional map of brain activation can be constructed providing information about brain regions involved in a particular function. The imaging

approach to the study of pain has led to the elucidation of a network of brain regions involved in the supraspinal response to pain, often referred to as the "pain matrix", and has provided the ability to associate the functions of these structures to particular aspects of pain.

Subjective pain ratings are also a primary tool that can offer insights into the processing of nociceptive information at the supraspinal level. Several pain rating scales and questionnaires have been created to measure the subjective experience of pain for use in both the clinical and experimental settings. Three of the most commonly used scales are the verbal rating scale (VRS), numerical rating scale (NRS), and the visual analogue scale (VAS) (Lara-Muñoz et al., 2004; Leon et al., 2004; Williamson & Hoggart, 2005; Ferreira-Valente et al., 2011; Hjermstad et al., 2011). The VRS is comprised of a list of descriptive terms that represent various levels of pain intensity, for example "no pain" or "moderate pain". Despite its reliability, validity, and ease of use, this scale is ordinal and has no interval relationship between descriptors. However, the NRS, which allows subjects to choose a number relative to verbal anchors, does exhibit interval properties and has also been validated as a reliable measure of subjective pain response. Finally, the VAS consists of descriptive verbal anchors, such as "no pain" and "most intense imaginable pain," at each extremity of a line that graphically represents the intensity of pain experienced. Pain rating is accomplished by marking the area on the line that corresponds to the subjective feeling. Although this method is slightly more cumbersome, in that it requires the use of a paper or computer, it exhibits ratio properties, is linear, and is strongly correlated with stimulus intensity. Studies have confirmed that, despite individual strengths and weaknesses, each of these three scales is a valid and reliable subjective measure of pain with significant positive correlations with stimulus intensity.

The scales described above provide a useful tool with which to examine the subjective nature of pain; however it is important to keep in mind that pain is a complex multidimensional experience. Studies have demonstrated a dissociation between the sensory and affective components of pain and have established the importance and necessity of using both pain intensity (sensory) and pain unpleasantness (affective) rating scales. Pharmacological and psychophysical research has revealed that while some manipulations primarily modulate the sensory component, as with distraction or administration of fentanyl, others act predominantly on the affective aspect, as seen with placebo or administration of diazepam (Fernandez & Turk, 1992; Auvray et al., 2010). Therefore, the implementation of both pain intensity and unpleasantness ratings is essential. Pain is, however, composed of not 2 but 3 components: sensory-discriminative, affective-motivational, and cognitive-evaluative. Experimental manipulations of cognitive factors, such as attention in the present research, allow for an investigation of the third component of pain and help to illuminate the neural mechanisms at play and produce a comprehensive understanding of the "pain" associated with the nociceptive event.

1.2.2 Spinal

The NFR is a widely used objective neurophysiological tool that has been demonstrated to correlate with subjective pain reports (Skljarevski & Ramadan, 2002; Sandrini et al., 2005). It was originally observed in animals as a withdrawal reflex of the ipsilateral limb following noxious electrical stimulation (Sherrington, 1910). Human studies of the NFR eventually identified two excitatory components of the NFR – RII and RIII, separated by a silent period. The first excitatory period, RII, reflects the tactile information conducted

via A-Beta fibers, whereas the RIII component is dependent on A-delta fibers, with a contribution from C fibers, and reflects transmission of nociceptive information. The RIII is a polysynaptic reflex that can be measured in humans by recording the EMG activity of the biceps femoris in response to nociceptive electrical stimulation of the sural nerve, in a temporal window of 90-180 ms following the shock (Sandrini et al., 2005). Because of the strong correlation between pain intensity and reflex size, the RIII has been used as an objective measure of pain in both clinical and experimental settings. The use of this method as a measure of spinal nociceptive transmission has proved invaluable to the study of the neural mechanisms underlying pain and the effect of various conditions on the modulation of pain processing and perception. However, despite numerous reports of a significant correlation between the objective measure of the NFR and subjective pain ratings, recent findings suggest that this correlation is not present under all conditions. Several studies have shown a dissociation between the RIII and pain ratings, putting into question its validity in the clinical setting. Despite this, it remains an important tool in experimental neurophysiology and provides an important method for the investigation of nociceptive transmission.

1.2.3 Autonomic

The autonomic system is highly interconnected with the nociceptive system, sharing many of the same brain regions involved in both the perception and modulation of pain, such as ACC, INS, periaqueductal grey matter (PAG), and ventrolateral reticular formation (VLM) (Benarroch, 2006; Leone et al., 2006). As such, measures of autonomic activity provide an important window into the influence of pain on the nervous system. The methods currently used in pain research that tap into autonomic functioning are GSR, HR, ECG, respiration rate

(RR), and BP. Studies have demonstrated a predictable increase in GSR and HR in response to painful stimuli. Additionally, the cardiac cycle, RR, and BP have been linked to subjective and objective measures of pain. Together, acquiring data on the supraspinal, spinal, and autonomic response to pain allows for a more comprehensive view of the neuroscience of pain.

1.3 Look here!!! The interplay between pain and attention

"Pain insists upon being attended to. God whispers to us in our pleasures, speaks in our consciences, but shouts in our pains. It is his megaphone to rouse a deaf world." (C.S. Lewis)Pain solicits attention; it directs focus to present or potential physical harm, thus affecting the relative salience of environmental stimuli. In turn, attention exerts a modulatory effect on pain. Attention plays a direct and important role in many cognitive and neurological functions including learning, memory, emotion, spatial processing, and sensory perception. It coordinates where and to what degree our focus is directed, thereby dictating how we sample and experience our environment. The interaction between attention and pain can therefore be described as a complex tug of war between competing stimuli and the constant reassessment of where to allocate biological and neurological resources.

1.3.1 Attention: Theories and Networks

The study of attention is historically important in the evolution of cognitive neuroscience and the emergence of experimental psychology. Furthermore, some of the first experiments in psychophysiology explored attention. The sustained interest in this domain is not surprising given the importance it plays in how we perceive the world around us. Attention is a complex dynamic equilibrium of lenses and filters through which we experience our

environment, both external and internal. It dictates what stimuli are highlighted and brought to the forefront of our experience, which percepts are ignored and how much weight is allotted to every attribute of our perception of reality.

The neurological underpinnings of the attention system are composed of three main anatomically and functionally distinct attentional networks that work together and influence processing systems. Three major components of attention– namely alerting, orienting and executive control – were initially identified and established as functionally discrete elements of attentional processing (Petersen & Posner, 2012). Alerting is defined as establishing (phasic alerting) and sustaining (tonic alerting) a state of increased vigilance; orienting is the prioritizing of the sensory input of a location or modality; executive control consists of control processes including error detection, conflict resolution, and decision-making.

More recent studies have revealed that these individual components of attention, while working together, are in fact dissociable. The Attention Network Test (ANT), a task created to isolate the components of attention, provided much support from human and animal studies for the idea that these systems function independently of one another. Fan and colleagues (2002) developed the ANT by combining a cued reaction time (RT) task with a flanker task(Fan et al., 2002). The objective of the task is to correctly identify the direction, left or right, of a central arrow located between four flankers. On some trials, cues are provided informing participants about the time and location of stimulus presentation. In this task, the influence of alerting is measured by the effect of providing a temporal cue on participant RTs, whereas orienting is reflected by changes in performance due to the presence of spatial cues. The involvement of executive functioning is established by differences in RT between trials with congruent and incongruent flankers.

The use of the ANT and variations of this task has led to the realization that individual differences in the strength of one component of attention are distinct from abilities of another and that improvements in functional capacity of one component are isolated from capabilities of another (Callejas et al., 2005). Moreover, pharmacological and imaging studies have demonstrated that these components of attention are not only functionally dissociable but are supported by anatomically distinct networks of brain structures and neurotransmitter systems (Petersen & Posner, 2012).

The alerting network has been revealed to rely on the norepinephrine (NE) system with projection from the locus coeruleus (LC) to frontal and parietal regions and lateralized to the right hemisphere. Pharmacological studies using drugs that influence the release of NE show that increased NE release improves alerting and decreased NE release inhibits the warning-signal effect (Morrocco and Davidson, 1998).

The orienting network on the other hand has been shown to rely on the cholinergic system. Studies with drugs that influence acetylcholine have an effect on orienting but not alerting (Davidson & Marrocco, 2000), further demonstrating a dissociation between these attention networks. Recent research suggests that orienting relies on two systems, a top-down dorsal system made up of the frontal eye fields and intraparietal sulcus/superior parietal lobe and a bottom-up ventral system involving the temporoparietal junction and ventral frontal cortex (Corbetta and Shulman, 2002).

The work of Dosenbach (2007, 2008) provides evidence for a dual network theory for the executive control system consisting of a frontoparietal system involved in moment to moment processing of a task, such as task switching/initiation and real-time adjustments, and a cingulo-operculum system, responsible for task set maintenance, acting as a stable background

for overall performance. Both systems act to produce top-down control. Together, alerting, orienting, and executive control networks support state of readiness, focal awareness, and complex mental operations, thereby influencing perception and cognition.

1.3.2 Effect of attention on sensory processing and integration

Our knowledge of the components of attention and the networks that support them is fundamental to our understanding of how we relate to external and internal environments. It is therefore important to consider the influence of attention on sensory processing and integration. Each component of attention influences sensory processing in a specific and unique way. Alerting facilitates the perception of stimuli by increasing overall arousal and/or acting as a warning signal in preparation for response to a target. Presentation of alerting cues has been shown to support improved ability to obtain information from a stimulus (Fernandez-Duque & Posner, 1997; Wang & Fan, 2007; Weinbach & Henik, 2012). Additional facilitation of information acquisition and processing is provided by the orienting component of attention. Orienting can be either a top-down or bottom-up selection of what information is most salient at any given time. The orienting network is responsible for both spatial and modality-specific allocation of attentional resources, acting as a spotlight on pertinent stimuli. Results from studies using a divided-attention task provide much support for this, showing enhanced ability to process information when orienting towards a relevant target and degraded performance when orienting away from the relevant target or towards another distractor target (Bashinski & Bachrach, 1980; Eriksen & Hoffman, 1973; Jonides, 1981; Mountcastle, 1978; Posner & Davidson, 1980; Nissen et al., 1978; Geffen & Wale, 1979; Sexton & Geffon, 1979; Mozolic et al., 2008). This is true of the influence of orienting for both location and modality of the

relevant stimuli. Finally, executive functioning influences sensory processing by highlighting and maintaining a stable background of task-relevant information and integrating this information in a meaningful way (reviewed by Jurado & Rosselli, 2007). Thus, attention and its various components play a critical role in how the sensory environment is sampled, processed, and integrated.

1.3.3 Attention and Pain

Pain is a sensory experience, and attention is well known to influence sensory processing and integration. Therefore, it is not surprising that attention has been shown to exert a powerful modulatory effect on pain. However, the neurological mechanisms underlying this modulation of pain by attention remain unclear. Several theories have been put forth to explain how attention influences pain, but a complete and comprehensive model of this interaction is still conspicuously unavailable.

Consider the processing of painful stimuli as the inner workings of a factory where several steps are required for the production of a final product, in this case pain. Modifications at any stage of the process will influence the outcome in specific ways. If, for example, the factory employees ignore arriving raw materials to be used in product manufacturing – directing attention away from painful stimuli - the result is a reduction in machine operation and less output of the final product - decreased activity in brain structures involved in sensory processing of pain and reduction of perceived pain intensity and unpleasantness. Here, attentional modulation of pain is the result of altered efficacy of processing of primary nociceptive inputs. One prominent theory of the attention-pain interaction suggests that, at least in part, the nociceptive system is influenced by attention in an equivalent manner to other

sensory modalities. If this is true, our understanding of the influence of attention on sensory processing would suggest that orienting towards the target stimulus, in this case pain, would enhance perception, whereas attention directed away from the target stimulus would decrease perception.

Bushnell et al. (1985) manipulated spatial attention (humans) and the modality (somatosensory or visual) to which attention was directed (monkeys) during sensory discrimination of innocuous and noxious thermal stimuli. In humans, subjects were provided with a visual cue (valid or invalid) indicating where to attend - left arm, right arm, or no cue - and instructed to detect the occurrence of a change in stimulus intensity. Ability to discriminate between stimuli - as measured by response latencies, percent undetected change, and percent early responses - was significantly better when subjects received cues as compared to without cues. Stimulus discrimination was also improved when cues validly indicated the location where the stimulus change occurred compared to invalidly cued trials. In monkeys, similar results were obtained when attention was manipulated between the visual and somatosensory modality. When attention was directed to the somatosensory as compared to the visual modality, monkeys' ability to discriminate between stimulus intensities (same performance measures as humans) was significantly improved. These attention-dependant performance differences in humans and monkeys were present for both innocuous warm (humans and one monkey) and noxious thermal trials. These data demonstrate that nociceptive and innocuous inputs are similarly modulated by direction of attention (location and modality), although they do not exclude the possibility of additional nociceptive-specific attentional processes.

In addition to altered capacity for the discrimination of noxious stimuli, perceptual differences resulting from attentional modulation would translate into a relative increase in perceived pain intensity when attending to a noxious stimulus and decreased perception of pain intensity when attending to other stimuli. In a study by Miron et al. (1989), participants performed a sensory discrimination task of visual and noxious thermal stimuli and provided pain intensity and unpleasantness ratings following each trial. Cues were provided on each trial indicating the modality in which the change would occur (directed attention) or that the change may occur in either modality (divided-attention). Participants' ability to discriminate a change in nociceptive stimulus intensity was dependent on direction of attention as evidenced by higher percent detection and greater speed of detection on correctly versus neutral and incorrectly signaled trials i.e. greater discriminability when attention was directed toward noxious stimuli. Additionally, pain intensity and unpleasantness ratings were also dependent on the attentional condition. Pain intensity and unpleasantness ratings were lower when attention was directed to the visual (falsely signaled trials) compared to the somatosensory modality (correctly signaled trials). Thus, Miron et al. (1989) replicated the effects of attention on the discriminability of noxious stimuli shown by Bushnell et al. (1985) and further demonstrated that attentional modulation also influences subjective pain perception.

In a magnetoencephalography study, Nakamura et al. (2002) investigated the effect of the degree of attention toward painful infra-red heat stimuli on S2 activity. Three conditions of attention to pain were examined: 1) low attention (subjects were instructed to ignore pain), 2) mid-level attention (subjects rated pain following an auditory tone), and high attention to pain (subjects associated a high or low tone with one of two pain stimulus intensities and were rewarded for accuracy). Low attention to pain resulted in less S2 activity compared to higher

attention to pain conditions. These results further support the idea that attentional modulation of pain is, at least in part, related to altered pain processing similar to perceptual attention-related changes in other sensory modalities. Therefore, attention-related changes in pain perception may result from direct modulation within areas related to the processing of noxious stimuli, or more indirectly as a result of the attentional modulation of sensory processing observed in other modalities – a redistribution of processing resources away from the nociceptive pathways.

A second theory on the attentional modulation of pain relates to higher order processing during execution of an attention task. In this case, to return to the factory analogy, if most factory workers are occupied with responsibilities other than product manufacturing, there will be a shift in which machines are operating, but there is a reduction in product output. In much the same way, resources being allocated to neural processing of an attention task will lead to increased activation of regions involved in task-related functions, decreased activity in pain processing structures, and decreases in pain intensity and unpleasantness ratings. In this case, pain perception is modulated as a result of resources being allocated differentially at the supraspinal level, resulting in a decrease in processing and integration of nociceptive information. Again, this prioritizing of neural processing of task-relevant information during an attention task mirrors the influence of attention on other sensory modalities. Dual-task interference studies demonstrate the limited capacity for neural processing when engaging in multiple tasks. These detriments in neural processing have been shown to occur at early sensory processing stages as well as later processing, integration and higher order functioning during performance of cognitive tasks (Kasper et al., 2008; Rissman

et al., 2009; Tombu et al., 2011). This effect of central processing bottlenecks is likely also involved in pain modulation during executive processing. Petrovic et al. (2000) examined the effects of engaging in a cognitive task on pain perception and brain activity using PET. Participants rated pain intensity induced by a cold-pressor test under two conditions: 1) pain alone, and 2) during performance of a computerized maze task. The pain-alone condition resulted in activation of characteristic pain-related regions including contralateral S1, bilateral S2, ACC, and INS. During the attention task, activity in somatosensory association areas and PAG/midbrain were significantly decreased and orbitofrontal regions increased. In conjunction with these changes in regional blood flow during performance of the attention task, participant's pain ratings were reduced. These results suggest that the increased activity during attentional processing of the cognitive task, such as in the PFC, may be involved in the modulation of pain processing and reductions in subjective pain ratings.

Empirical support for these theories notwithstanding, there is evidence for a third pain-specific neural mechanism of attentional modulation. In this case, if the factory manager issues a memo to order a stop on incoming raw materials or to turn on/off some machines, there will be a shift in machine operation and a subsequent decrease in production of the product. Here, the performance of a distracting task may engage higher order structures initiating descending inhibition (or facilitation) of pain processing at the spinal level or altering activity at the supraspinal level which leads to increased activation of regions involved in attentional processing, decreased activity in pain processing structures, possible changes in activity of additional structures, and decreases in pain intensity and unpleasantness ratings.

Recent imaging studies on attention-mediated changes in brain response to pain provide insight into the mechanisms at play and suggest that, in addition to attentional modulation processes involved in other sensory modalities, pain-specific mechanisms – including descending inhibitory systems - may be recruited. Valet et al. (2004) used fMRI to examine the attentional modulation of pain by the Stroop task. In comparison with the pain-alone condition, performance of the Stroop task resulted in significantly increased activation of the orbitofrontal cortex, perigenual ACC, PAG, and posterior THAL, as well as decreased pain ratings. Additionally, distraction resulted in reductions in the activity evoked from pain alone, particularly in the medial THAL, the midcingulate, anterior-ventral INS and lateral PFC. Moreover, Valet et al. (2004) report a functional interaction between these structures during the distraction task suggesting that these regions mediate the observed changes in pain processing and related reductions in pain ratings.

Tracey et al. (2002) used high-resolution fMRI to investigate PAG activity during attention to pain compared to distraction from pain. During the attention to pain condition, participants were instructed to focus on the pain whereas in the distraction condition, participants were instructed to think of something other than the painful stimulus. During the distraction condition, PAG activity was significantly higher and correlated with reductions in pain ratings. In conjunction with other studies that report increased activity in frontal cortex regions and PAG and reductions in S1 and S2, with related decreases of subjective pain ratings when participants attend away from painful stimuli (Nakamura, Paur, Zimmermann, & Bromm, 2002; Peyron et al., 1999; Bantick et al., 2002), these results suggest that attentional modulation of pain involves a descending modulatory system.

In a recent study, high resolution fMRI of the spinal cord during a high- versus low-working memory load distraction task with concurrent application of thermal pain resulted in reductions of neuronal response to pain in the dorsal horn and paired decreased pain ratings, suggesting the involvement of a descending inhibitory system in attentional modulation of pain (Sprenger et al., 2012). In a second experiment, administration of naloxone, an opïoid antagonist, partially blocked this effect, demonstrating that the observed changes were partly due to an endogenous opïoid-mediated analgesia. Taken together, this may suggest the contribution of a descending opïoid-mediated system in the attentional modulation of pain. However, it remains possible that these reported changes in nociceptive processing are due to stress-related pain modulation, which has been associated with descending opïoid-mediated inhibition of nociceptive responses and is often not considered in studies on attentional modulation of pain. As such, in order to address this potential confound, the paradigm in the study presented in this thesis manipulates stress levels independently from the attention task, thereby dissociating the effects of stress from that of attention on pain processing.

1.3.4 Stress, Attention and Pain

Stress is an important factor to consider in the investigation of the attentional modulation of pain. Research over the past three decades has demonstrated that stress typically has a suppressive effect on pain (Butler & Finn, 2009). This psychological modulation of pain, commonly referred to as stress-induced analgesia (SIA), has received much interest. The anatomical, molecular, and neurochemical mechanisms (including the contribution of opïoid and non-opïoid mediated systems) underlying SIA have been largely investigated. However, despite the overwhelming evidence from numerous animal and human studies supporting an

analgesic effect of stress, a number of investigators have reported increases in pain during exposure to stress – stress-induced hyperalgesia – a phenomenon that is still not well understood (Imbe et al., 2006; Richebe et al., 2011).

Given the significant modulatory effect of stress on pain, it is important to control for the influence of this factor during the investigation of other types of psychological modulation of pain. Unfortunately, the effects of stress appear to have been overlooked in many studies on attentional modulation of pain, and this may provide an explanation for some seemingly contradictory findings in the literature. One major cause for this is the stressful nature of some of the currently used attention/distraction tasks. In fact, some of the same tasks used as a "distraction task" in the study of attention, including mental arithmetic, the Stroop, tracing tasks, and other cognitive tasks, have been employed in research on stress as a "stress manipulation." Regrettably, there is no quick fix to this issue, as highly demanding and engaging tasks that require focused attention are, by the nature of the task, stressful to some degree. One possible solution to this caveat is to differentially modulate stress and attention levels in an attempt to dissociate the involvement of each factor in the modulation of pain. Varying the difficulty level of the attention task would have the effect of altering stress and attention in parallel. Alternatively, an experimental manipulation of stress that is separate and distinct from the attention task could potentially modulate these psychological factors differentially and may help dissociate their effects.

1.3.5 Attention, Pain, and the RIII

Previous research has demonstrated that many physiological, pharmacological and psychological factors modulate both spinal and supraspinal levels of pain processing (Sandrini

et al., 2005). Although there is evidence that attention has a modulatory effect on pain - increased pain while attention is directed towards and decreased pain while attention is directed away from a noxious stimulus - the neural mechanisms underlying these changes remain unclear. The NFR, or RIII reflex, provides a method with which to examine the effects of attention on spinal nociceptive transmission to gain insight into the neural underpinnings of the observed changes in pain processing. The RIII has been utilized in pain research as an objective measure of spinal nociceptive transmission and has been shown to correspond with subjective pain ratings, making it a useful tool in clinical and experimental settings. However, recent work has demonstrated that the relationship between these measures does not always correlate, suggesting a possible dissociation between RIII and subjective pain ratings (Roy et al., 2011).

The current literature on the effects of attention and distraction on pain ratings and the RIII is inconsistent. Bathien and colleagues (1969, 1971, and 1972) found that certain, but not all, tasks that demanded the attention of participants resulted in a change in RIII amplitude. Willer et al (1979) showed that both pain sensation and RIII were inhibited during a mental task, whereas Dowman (2001) found that attentional set reduced pain ratings but had no effect on the RIII. Some more recent studies have been unable to replicate a modulatory effect of attention on the NFR, finding no significant difference in RIII threshold during a distraction task (France 2002, Terkelsen 2004, Hennighasuen et al 2007). Further research on the effects of attention on the RIII reflex and pain have yet to resolve these incongruencies.

The conflicting findings in the literature on attentional modulation of the RIII reflex and pain are due to several factors, both methodological and theoretical. First, as previously mentioned, a likely confound in a number of studies is the effect of stress on pain mechanisms.

Several studies examining the neural mechanisms underlying the effect of attention on nociception and pain made use of stress-inducing tasks such as mental arithmetic (Bathien & Hugelin, 1969; Bathien, 1971; Bathien & Morin, 1972; Willer et al., 1979; France et al., 2002; Terkelson et al., 2004; Edwards et al., 2006; McIntyre et al., 2006). Because stress has a modulatory effect on pain at the spinal and supraspinal levels, failure to control for stress level induced by distraction tasks hinders the interpretation of findings from these experiments. Additional studies have introduced other confounds such as emotion and expectancy, processes that have been shown to modulate both the RIII and pain ratings (Willer et al., 1979; Ruscheweyh et al., 2011), thereby obscuring the evaluation of the findings from these experiments. Additional methodological issues, such as variations in the intensity of stimulation of the sural nerve between studies, further obfuscate analysis of the results. Several studies stimulate at threshold intensity of the reflex (Edwards et al., 2006), while others have selected an intensity of 1.5 times the threshold (Terkelsen et al., 2004) and still others report using an unspecified level between threshold and tolerance (Dowman, 2001). This is of considerable concern since the level of stimulus intensity may affect the susceptibility of the NFR to modulation by cognitive factors. Additionally and importantly, the current literature fails to consider the multifaceted nature of the attention system, which is composed of several functionally and anatomically dissociable networks: alerting, orienting, and executive control. These components of attention may produce distinct effects on nociception and pain and may involve different underlying modulatory neural mechanisms. Overall, the current literature on attentional modulation of nociception and pain is confusing, inconsistent, and consequently largely uninterpretable.

1.4 Objectives

The present work aims to explain the conflicting findings in the literature on the attentional modulation of pain perception and NFR in order to gain further insight into their causal neural mechanisms. An in-depth review of the existing literature on attentional modulation of the RIII and pain was undertaken to critically analyze the current findings and generate hypotheses that may help clarify the ostensible contradictions (see general discussion). The development of these hypotheses into a novel functional framework along with the conception and execution of a study to test them constitute the focus of the current work.

In the present study, a component-based approach to the investigation of attentional modulation is proposed that separately examines the effects of alerting, orienting, and executive control on nociception and pain and includes stress as an additional variable. We isolated the components of attention in a discrimination task involving both visual and somatosensory stimuli. Throughout the experiment we measured the RIII reflex, skin conductance response (SCR), and pain ratings in response to painful electrical stimuli delivered to the sural nerve in order to examine the effects of these components of attention on nociception and pain. Furthermore, we made use of two previously validated methods to manipulate basal stress levels (music-induced relaxation and the Trier Social Stress Test: TSST) to dissociate the influence of attention and stress on pain processing. Exposure to music reduces anxiety and stress and has been shown to reduce subjective and physiological indices of stress such as heart rate, blood pressure, and the cortisol response to exposure to an external stressor (Knight & Rickard, 2001; Khalfa et al., 2003; Salamon et al., 2003). The

TSST has been demonstrated as a reliable procedure to increase subjective stress reports and salivary cortisol measures via motivated performance with social-evaluative threat and uncontrollability (Kirschbaum et al., 1993; Dickerson & Kemeny, 2004).

Chapter 2: Article

Effects of components of attention and stress on pain and the nociceptive flexion reflex

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Abstract

The literature on attentional modulation of the nociceptive flexion reflex (NFR) and pain is inconsistent, possibly because the complex nature of attention processes and the possible interactions with stress have been overlooked. Here, the NFR and pain ratings were measured before and during a visual and somatosensory delayed-discrimination task designed to separate components of attention-related processes (alerting, orienting, and sensory working-memory), in three groups of healthy individuals following relaxation, stress-induction, or no manipulation (control). Pain was significantly reduced following stress-induction, consistent with stress-induced analgesia while effects of attention components were observed mainly or only in the relaxation group. Alerting reduced both pain and the RIII. Top-down orientation away from noxious stimuli resulted in hypoalgesia (pain ratings) independent from the stimulus modality. In contrast, the NFR was larger when attention was directed towards the visual compared to the somatosensory modality. Beyond these orientation effects, executive control (working memory) had no additional effect on pain but showed a tendency to decrease further the NFR relative to baseline. The modulation of nociception by attention was observed only in the low-stress group. These findings highlight the influence of each component of attention on pain and the masking effect of stress on some of these modulatory effects. The spatially- and modality-specific nature of attentional modulations of pain and the NFR, respectively, further demonstrate the complexity of attentional influences on perceptual and spinal processes and clearly points to the multiplicity of underlying mechanisms.

Introduction

Psychological processes have been demonstrated to have a powerful modulatory effect on pain and nociception. Cognitive modulation of pain has been shown in studies on hypnosis, placebo, emotion, and attention (Price et al., 2004). The current literature on the effects of attention on both pain and nociception, however, is inconsistent. Early studies on the attentional modulation of spinal nociceptive transmission, as measured by the nociceptive flexion reflex (NFR), found either a decrease or no change in the reflex amplitude during performance of an attention task and, in one case, a slight increase in reflex amplitude (Bathien, 1971; Bathien & Hugelin, 1969; Bathien & Morin, 1972). Research on the effects of an attention task on both pain and spinal nociceptive transmission has yielded similarly equivocal results. Where some findings indicate a decrease in both pain and NFR (Willer, Boureau, & Albe-Fessard, 1979), others have found no change in NFR threshold or amplitude with variable findings on pain ratings (Dowman, 2001; France, Froese, & Stewart, 2002; Terkelsen, Andersen, Molgaard, Hansen, & Jensen, 2004). Others still have reported a decrease in pain ratings and concurrent facilitation of spinal nociceptive transmission (Louisa Edwards & Richard Clarke, 2006; McIntyre, Edwards, Ring, Parvin, & Carroll, 2006; Roy, Piche, Chen, Peretz, & Rainville, 2009). A more refined analysis of attentional processes involved in the modulation of pain and the NFR may help clarify these contradictory results.

Attention is a complex process involving several components: alerting, orienting and executive control. Behavioural and imaging studies have revealed that these components of attention are functionally dissociable from one another and involve distinct neural mechanisms (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005). To our knowledge, no study has systematically investigated the specific influence of each component of attention on pain and the

NFR. Moreover, the modality and location to which attention is being directed needs be considered (e.g. visual or somatosensory; close to, or away from, the painful site). Furthermore, another dimension of psychological processing rarely accounted for across these studies is the effect of stress (task-related or unrelated). This is an important factor to consider as cognitive tasks are sometimes used to generate psychological stress and stress may modulate pain-related brain responses (e.g. Vachon-Presseau, 2013). Therefore, the individual components of attention, the sensory modality of the distracter, and the influence of stress must be accounted for in order to disentangle the conflicting literature on the modulation of the NFR and pain by attention.

This study employs a delayed-discrimination task designed to dissociate components of attention involved in alerting, orienting, and executive processes (here sensory working-memory). We examined the effects of these components in the visual and somatosensory modalities while varying the levels of both task-induced and social stress across subjects. In so doing, this research provides a novel conceptual model of how attentional mechanisms affect the spinal transmission of nociceptive signals and the perception of pain. Moreover, by dissociating the components of attention across sensory modalities and stress levels, these results might explain some of the inconsistencies in the literature on the attentional modulation of spinal nociceptive transmission and pain.

Materials and Methods

Participants

Thirty-eight healthy volunteers between the ages of 18-35 were recruited from the University of Montreal using on-campus notices, from Concordia University via their website, and through general internet advertisement. Five participants were excluded due to an inability to

obtain a stable RIII reflex and pain ratings. Of the thirty three remaining subjects, three were excluded because they did not complete the entire experimental protocol (1 participant withdrawal and 2 technical failures). Additionally, one participant was excluded post hoc due to an elevated Becks Depression Inventory-II (BDI-II) score (BDI-II score = 31). The final sample included 29 healthy volunteers aged between 20 and 35 years (25.6 ± 4.5 years; 15 men and 14 women) with no history of chronic pain, diabetes, colour-blindness, neurological or psychiatric disease. The experimental protocol was approved by The Research Ethics Board of the "Centre de recherche de l'Institut de gériatrie de Montréal"; all participants completed a consent form and were compensated for their participation.

Study design

The study relied on a mixed experimental design involving the manipulation of stress across three groups (high stress, relaxation/low stress, and control) and the manipulation of attention within-subject. Pain and NFR responses were assessed before (baseline) and throughout the different phases of an attention task. Stress was induced by the Trier Social Stress test (TSST) administered before the attention task and by additional negative feedback on task performance. Low stress was induced by listening to relaxing music prior to the task and supportive feedback on task performance. This design allowed us to assess effects of stress on pain and NFR responses at baseline (no task), the effects of different functional components of attention (see task description, below), and the potential interaction between stress and attention.

Painful Electrical Stimulation and NFR measurement

Transcutaneous electrical stimulation was administered to the left sural nerve with a Digitimer DS7A constant-current stimulus-isolation unit (Digitimer Ltd, Welwyn Garden City, Herfordshire, UK) triggered by a train generator (Grass Medical Instruments, Quincy, MA, USA) in the form of 10 rectangular 1 ms pulses delivered over a 30 ms period (333 Hz) and controlled by a computer running E-Prime2 (Psychology Software Tools, Sharpsburg, PA, USA). Participants were seated with their knee flexed at 120˚ and ankle at 90˚ and the location of electrode placement was shaved, rubbed with a slightly abrasive gel to insure adequate conductance, and sterilized with alcohol swabs. Electromyographic (EMG) electrodes were placed at the brevis head of the biceps femoris muscle and the stimulation electrodes placed over the retromaleolar path of the left sural nerve. EMG responses to electrical stimuli were recorded using a MP150 system (Biopac Systems Inc.; EMG100C amplifier and EL503 Ag-AgCl disposable electrodes; low pass 500Hz, high pass 10Hz, notch filter 60hz). Reflex threshold was determined using the staircase method (Willer, 1977) and defined as a stimulus that elicits a detectable EMG response on 50%-80% of trials in a temporal window of 90-180 ms post-stimulus. Stimulus intensity was then set individually to 120-140% of the reflex threshold for the remaining of the experiment. The signal was processes using the RMS transformation and mean smoothing. The integral of the transformed signal was taken 90ms to 180ms after the stimulus onset to quantify the RIII response.

Attention Task

The attention task consisted of a sensory delayed-discrimination task in the visual and somatosensory modalities in which alerting, orienting, and executive control (working memory) were separated temporally. The task design was developed to dissociate these three components

of attention and further included conditions to assess the effect of spatial attention (i.e. attending toward or away from a painful stimulus). Additionally, this design was developed to distinguish the effects of attending to the visual versus somatosensory modality.

Participants were seated comfortably in a partially reclined position approximately 1 m from a computer screen. All slides in the experiment consisted of a cartoon image of a computer, a left foot, and a right foot (Fig.1). Colour (red or green) and shape (circle or square) around the images indicated specific parts of the trial. All trials were separated by a rest period, the intertrial interval (ITI), designated by all images circled in red. The alerting phase started when the circles surrounding the images turned green to signal the beginning of a trial. This was followed by the orienting phase, during which a cue indicated which target stimulus (i) should be attended to perform the delayed-discrimination task. The direction of attention was cued with one (directed attention) or all (divided attention) of the green circles changing into squares. In all conditions, vibrotactile stimuli were then presented simultaneously to both feet while the luminance of the background of the image was changed for a period of 1000ms. This was followed by a variable inter-stimulus interval (ISI) (working-memory or executive phase) after which a second set of stimuli were delivered again for a duration of 1000ms. At this time, participants indicated by key press whether or not they detected a change in the intensity of the cued stimulus (as indicated by the green square) with a maximum response period of 4000ms. If a response was not given within the 4000 ms period, feedback was provided indicating that their response was too slow. Additionally, feedback was provided immediately following each response indicating a correct or wrong answer. A response time of less than 200 ms was considered an early response and reported as an error. All phases of trials (ITI, alerting, orienting, and ISI) lasted for variable durations of 1000, 2000 or 3000 ms (pseudorandomized order).

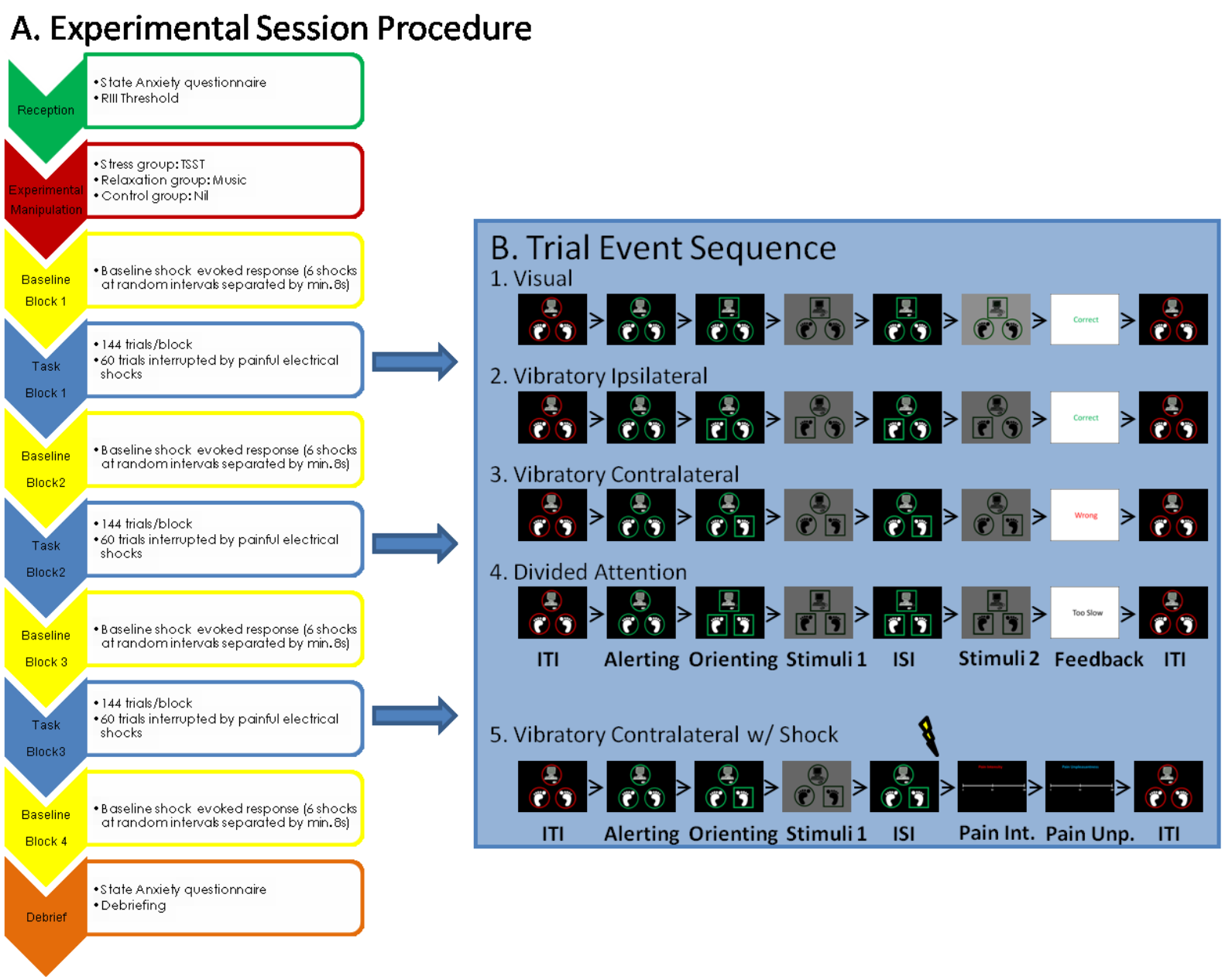
A. Experimental Session Procedure
Reception
•State Anxiety questionnaire
•RIII Threshold
Experimental Manipulation
•Stress group: TSST
•Relaxation group: Music
•Control group: Nil
Baseline Block 1
•Baseline shock evoked response (6 shocks at random intervals separated by min. 8s)
Task Block 1
•144 trials/block
•60 trials interrupted by painful electrical shocks
Baseline Block2
•Baseline shock evoked response (6 shocks at random intervals separated by min. 8s)
Task Block2
•144 trials/block
•60 trials interrupted by painful electrical shocks
Baseline Block 3
•Baseline shock evoked response (6 shocks at random intervals separated by min. 8s)
Task Block3
•144 trials/block
•60 trials interrupted by painful electrical shocks
Baseline Block 4
•Baseline shock evoked response (6 shocks at random intervals separated by min. 8s)
Debrief
•State Anxiety questionnaire
•Debriefing
B. Trial Event Sequence
1. Visual
Correct
2. Vibratory Ipsilateral
Correct
3. Vibratory Contralateral
Wrong
4. Divided Attention
Too Slow
ITI
Alerting
Orienting
Stimuli 1
ISI
Stimuli 2
Feedback
ITI
5. Vibratory Contralateral w/ Shock
ITI
Alerting
Orienting
Stimuli 1
ISI
Pain Int.
Pain Unp.
ITI

Figure1. **Experimental Paradigm.** (A) Experimental session procedure. Following reception (green), experimental manipulation was performed based on stress group (red). 4 baseline blocks (yellow) were interleaved with task blocks (blue) and subjects were debriefed (orange) at the end of the session. (B) Trial event sequence. The 3 task blocks were composed of 4 trial types: (1) visual trials; (2) vibratory ipsilateral trials; (3) vibratory contralateral trials; (4) divided-attention trials. Trials followed the same sequence of events of alerting, orienting, stimuli 1, ISI, stimuli 2, and feedback – unless interupted by a shock (42% of trials) e.g. : (5) vibratory contralateral trial with shock during ISI. Shocks were immediately followed by ratings of pain intensity (Pain Int.) and pain unpleasantness (Pain Unp.). All trials were seperated by ITIs of variable duration (1000, 2000, or 3000ms). For additional details see materials and methods.

Vibrotactile and Visual Stimuli

Pilot testing was conducted to determine stimulus parameters for vibrotactile and visual stimuli. Vibrotactile stimuli were generated by a custom-made vibrotactile stimulator that converted sound files to vibration outputs. All stimuli were composed of 85Hz sinusoidal sound waves created with Test Tone Generator (Digital River GmbH, Vogelsanger Str. 78, D-50823 Cologne, Germany). Maximum stimulus intensity was obtained from the maximum output volume of the computer used to run the attention task program. Stimuli were delivered to the soles of the feet and elicited an innocuous vibrotactile sensation. Five stimulus intensities, each separated by10dB increments, were employed to produce 4 degrees of magnitude difference from the baseline level.

Visual stimuli were created with Microsoft Power Point 2007. Background luminance of stimuli was adjusted by altering the brightness setting of the original white background image. Five levels of background luminance of visual stimuli were employed to produce 4 degrees of magnitude difference from the baseline level. Baseline was set as a 60% decrease in brightness and subsequent levels were set as 56, 52, 48 and 44% decrease from the original image.

Stress Manipulation

High-Stress Group

Participants assigned to the high-stress group underwent a series of experimental manipulations to induce psychosocial stress. These manipulations have previously been shown to result in a subjective feeling of stress and an increase in salivary cortisol levels (Dickerson & Kemeny, 2004). Following RIII reflex thresholding, participants engaged in the TSST (Kirschbaum et al, 1993). Prior to starting the first block of the attention task, subjects were informed that throughout the remainder of the experiment their task performance would be monitored by a panel of experts located in another room (confederates who administered the TSST). They were instructed that their behaviour would also be recorded via video equipment set up in the room and that this would be scrutinized by behavioural analyst specialists during and following the experiment. Additionally, the experimenter provided negative feedback following each block of the attention task and instructed subjects to improve performance on the task. This feedback was given independently of the participant's performance.

Relaxation/Low-Stress Group

Participants in the relaxation/low-stress group listened to 13 minutes of relaxing music in order to reduce stress levels and induce a state of relaxation. At the end of each block of the attention task, subjects in this group were provided with positive feedback. This feedback was given independently of the participant's performance.

Control Group

Participants assigned to the control group did not undergo any psychological manipulation. No verbal feedback on task performance was provided following blocks of the attention task.

Procedure

The experiment was composed of two sessions; a preliminary session (approx. 1 hr.) and an experimental session (approx. 3 hrs.) separated by a minimum of 24 hours. Prior to the experimental session, participants were allocated to one of three experimental groups (control, relaxation/low-stress, or high-stress), balanced for age and sex. All participants completed the same protocol during the preliminary session and returned for a second visit to carry out the experimental session.

Preliminary Session

Upon arrival, subjects provided written informed consent to participate in the study and completed three questionnaires (State (SAI) and Trait Anxiety Inventory (TAI), BDI-II, Pain Catastrophizing Scale) and a basic information form. RIII-reflex threshold was determined by the staircase method with 4 ascending and 4 descending sets of transcutaneous electrical stimuli; subsequently, subjects received 120-140% of their reflex threshold throughout the experiment. A brief assessment of sensitivity to innocuous vibrotactile stimuli applied to the sole of both feet was performed to ensure adequate discrimination ability for the attention task used in the study design. Detailed instructions were provided explaining the task, followed by a brief practice session (5 trials of each condition) with no electrical stimulation, in order to familiarize subjects with non-painful experimental stimuli and ensure adequate understanding of the task. A second

practice block was performed, including painful electrical stimuli, to ensure participants were sufficiently familiar with the entire experimental protocol.

Experimental Session

The second session of the experiment began with the completion of the SAI and RIII-reflex thresholding. Participants then engaged in the experimental manipulation specific to the group (relaxation, stress, or control). This was followed by the collection of a second saliva sample and administration of 6 painful electrical shocks (baseline block). Subsequently, all participants completed 3 blocks of trials of the attention task. Each block consisted of 144 trials, 60 of which were interrupted by a painful electrical shock to the sural nerve; i.e. 42% of trials distributed across the different phases of the task in a pseudorandom order. If a painful electrical shock was delivered, the attention task was interrupted and the participants rated the pain intensity and pain unpleasantness on a visual analog scale (VAS) of 0-100 displayed on the computer screen. Ratings were reported with a key press after guiding a visual cursor to the desired position on the scale using the index and middle fingers. An additional baseline condition (6 shocks) was administered prior to the onset of each block. Skin conductance response (SCR) was monitored throughout the experiment with galvanic skin response (GSR). Additionally, participants were provided with verbal feedback on their task performance at the end of each block (based on their group). At the end of the third block, a last baseline block of 6 shocks was completed followed by a second SAI. Following the experiment, participants were debriefed on the purpose of the study and experimental manipulations conducted and were compensated for their participation.

Data Analysis

Task Performance

To confirm participants performed the attention task and attended to the expected target location, mean reaction times and response accuracy (hits and false alarms) were calculated for each experimental trial type uninterrupted by a shock stimulus. Performance was compared across trial types (modality and magnitude difference between stimuli) using repeated measures analysis of variance (ANOVA) and follow-up repeated contrasts of successive levels.

RIII Reflex, Pain Ratings and SCR

RIII reflexes and SCRs were visually inspected prior to data analysis to identify and remove artefacts or exclude the corresponding trial from the analysis. Each dependent data set, including ratings, was assessed and preprocessed to control data range, normality, and homogeneity of variance, test for statistical outliers, and correct for sphericity prior to statistical analyses (see Supplementary Figure S1). If necessary, transformations were applied to meet basic conditions of ANOVA (SCR and pain intensity were transformed using the square-root and the RIII using log). A total of 0.35% pain ratings, 0.59% RIII, and 9.4% SCR were excluded due to technical problems or extreme values (>3sd).

Analyses of the effects of attention on these dependent variables were performed in three steps, each including the Group as a between-subject variable. First, the overall effect of engaging in a task was examined by comparing the mean response in the attention task blocks (across all attention conditions) to the mean baseline acquired between task blocks using a Group (3) x Block (2) ANOVA. In the second analysis step, the effects of the three components of attention were assessed by comparing the alerting, orienting and inter-stimulus interval

(working-memory) phases of the task to the inter-trial interval. We examined these effects using a Group (3) by Component (4) ANOVA. In the third analysis step, we decomposed the orienting and ISI phase according to the direction of attention (Direction) cued to the left foot, right foot, computer monitor or across all three potential targets (i.e. divided attention). The effect of the attention process (Attention: orienting vs. working-memory) and attention direction (Direction) was tested using a Group (3) by Attention (2) by Direction (4) ANOVA. Planned comparisons were conducted to test *a priori* hypotheses. When required (sphericity), the degrees of freedom were adjusted with the Greenhouse-Geisser correction (Supplementary Fig. S1). The attention effects that were significant for pain intensity were also significant for pain unpleasantness, therefore only pain intensity results are reported.

Results

Manipulation Checks

Manipulation checks were carried out to confirm participants adequately performed the attention task and directed their attention to the appropriate target(s) (see Supplementary Tables S1 and S2). There was no significant effect of group on task performance (response rate and accuracy). Overall accuracy of performance on the task was 77.57% correct responses, indicating that the participants were performing the task and that it was challenging enough to solicit sustained attention. Performance decreased with increased difficulty level (i.e. smaller difference between discrimination stimuli), as evidenced by increases in reaction times (RT) and decreases in correct response rates. RTs were shorter for visual than somatosensory trials, and the same trend occurred in the divided attention trials, replicating a typically observed physiological

property of response times to stimuli from different modalities. Divided-attention trials produced lower correct response rates and tended toward higher RTs in the visual and right-foot condition than single target trials of the same target location ($p<0.05$). There was no significant difference in mean accuracy between visual and somatosensory trials. These results confirm that participants were engaged in the task and attended to the cued target location.

Effects of Stress on Attentional Modulation of Pain-related Responses

The current study manipulated stress level between subjects in order to examine the effect of stress on attentional modulation of pain-related responses. First, we examined the effect of the experimental stress manipulation on pain ratins by comparing pre- and post- stress/relaxation manipulations (see Supplementary Figure S2). There was no main effect of group on pain intensity ratings ($F(2,26)=0.5, p=0.6$), however, there was a significant effect of the experimental manipulation which was dependent on the group (interaction : $F(2,26)=3.59$, 0.04). Decomposition of the effect revealed that the stress-induction resulted in a decrease in pain intensity ratings ($F(1,8)=5.53$, $p=0.05$), whereas there was no change in either the control group ($F(1,9)=0.08$, $p=0.8$) or the relaxation group ($F(1,9)=0.1$, $p=0.7$). Stress-induced analgesia (SIA) is a phenomenon that has been consistently demonstrated throughout the literature on the supraspinal modulation of pain. Here, we replicated the characteristic findings of SIA, showing that our stress-induction manipulation significantly reduced pain intensity ratings whereas relaxation and control groups showed no significant changes in pain ratings between pre- and post-measurement periods.

Second, we examined the influence of stress on attentional modulation of pain processes by including stress as a between-subject factor in all of the following analyses which focused on

the effects of attention on pain-related responses (Table 1 summarizes the results of the main statistical analyses). There was no main effect of group on outcome measures in all of the following analyses.

Engagement in a Task

The effect of engaging in a task was assessed by comparing the mean response in the attention-task blocks (across all attention conditions) to the mean baseline acquired between task blocks. Overall engagement in the task resulted in a significant decrease in mean RIII reflex amplitudes ($F(1,26)=16.91$, $p<0.001$) (Fig.2A). There was no significant overall effect of task engagement on pain intensity ($F(1,26)=0.39$, $p=0.5$) (Fig.2B). Both stress ($F(2,24)=0.038$, $p=1.0$) and overall effect of performing the task ($F(1,24)=0.7$, $p=0.4$) had no effect on shock-related SCR (Fig.2C). In summary, the overall effect of task engagement suppressed the RIII reflex but did not significantly modulate pain or SCR. However, the absence of global modulation of pain and SCR by the task is due to the variation between trial conditions, specifically the inclusion of trials where attention is directed toward or away from the site of painful electrical stimuli (towards and divided attention conditions) (see Supplementary Figures S3 and S4).

Table 1. Summary of ANOVAs of RIII reflex, pain ratings, and SCR on transformed data for all experimental conditions.

	RIII Reflex (log)			Pain Intensity (sqrt)			SCR (sqrt)		
	df	F	*p*	*df*	F	*p*	*df*	F	*p*
Task Engagement									
Block	1,26	16.91	<.001*	1, 26	0.39	0.5	1, 24	0.71	0.4
Block X Group	2,26	1.54	0.2	2, 26	1.15	0.3	2, 24	0.26	0.8
Group	2,26	0.23	0.8	2, 26	0.2	0.8	2, 24	0.04	0.9
Components of Attention									
Attention	3,78	3.38	0.02*	2.3, 57.1	2.35	0.08	1.6, 37.9	1.15	0.3
Attention X Group	6,78	4.84	<.001*	4.6, 57.1	0.71	0.6	3.2, 37.9	1.01	0.4
Group	2,26	0.32	0.7	2, 2	0.54	0.6	2, 24	0.13	0.9
Direction of Attention and Attention Process									
Attention	1,26	3.49	0.07	1, 26	0.03	0.9	1, 24	1.45	0.2
Attention X Group	2,26	0.50	0.6	2, 26	0.79	0.5	2, 24	0.42	0.7
Direction	3,78	5.85	0.001*	2.2, 57.5	3.29	0.04* [a]	3, 72	1.94	0.1
Direction X Group	6,78	2.91	0.01*	4.4, 57.5	1.16	0.3	6, 72	0.57	0.7
Attention X Direction	3,78	0.85	0.5	2.2, 58.2	1.523	0.2	3, 72	4.317	0.007*
Attention X Direction X Group	6,78	0.381	0.9	4.5, 58.2	1.51	0.2	6, 72	1.623	0.1
Group	2,26	0.26	0.8	2,26	0.215	0.8	2,24	0.083	0.9

*Significant effects.

[a] Effect also significant for pain unpleasantness (p=0.03).

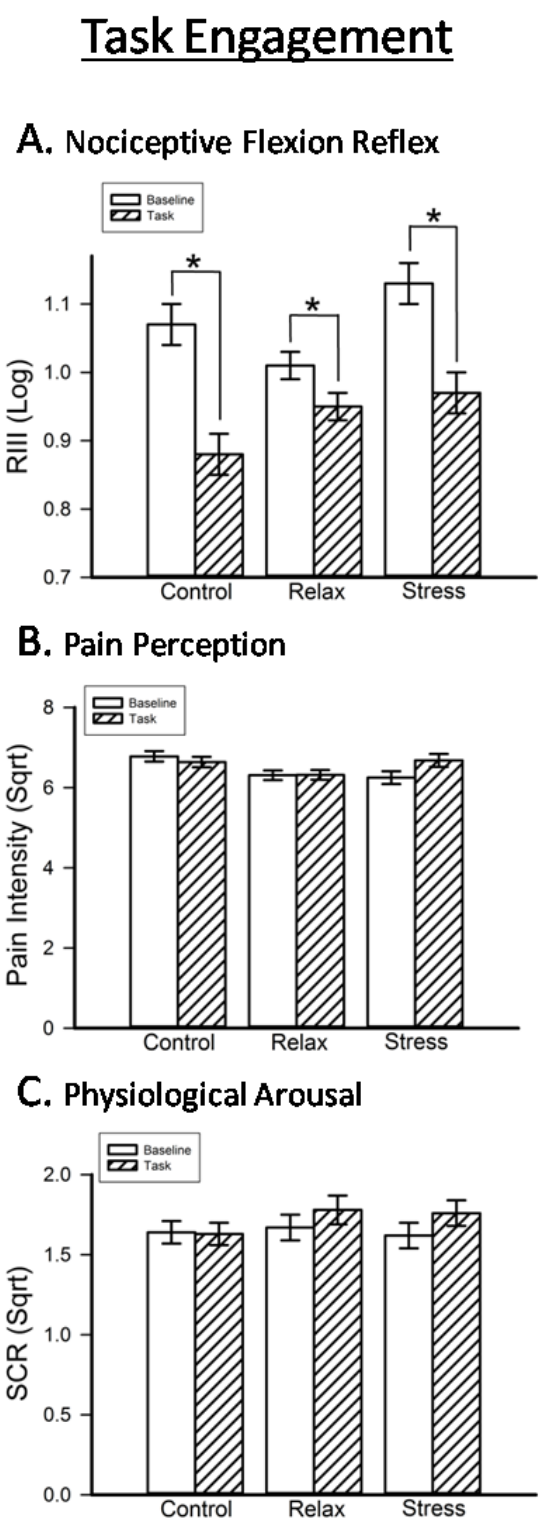

Figure 2. **Engaging in the task produces a significant decrease in NFR (A) in all three stress groups.** No effect of task engagement was produced for pain intensisty (B) and physiological arousal (C). Error bars represent SEM adjusted to reflect within-subject variance (see Cousineau, 2005). *(p<0.001)

Components of Attention: Alerting, Orienting & Working-memory

Pain responses in each of the three phases of the task were compared to the responses recorded during the ITI and across the three groups (see statistical results in Table 1). The main finding was a significant effect of stress level on the attentional modulation of the RIII reflex (Group X Component interaction: $F(6,78)=4.84$, $p<0.001$). Decomposing the interaction revealed that orienting and working-memory components resulted in a decrease in the reflex amplitude compared to the ITI (Fig.3A), but this was only true for the relaxation group ($F(3,27)=10.2$, $p<0.001$). There was no effect of the alerting condition compared to the ITI on RIII reflex amplitude for any group. By comparing mean attention task components (alerting, orienting and working memory), our results show that the modulation of the RIII reflex by attention is dependent on orienting and working-memory components and that this attentional modulation is sensitive to stress level, with stress inhibiting the attention-related suppression of the NFR.

We found no significant difference in pain intensity compared to ITI (Fig.3B), nor any significant change in SCR (Fig.3C), resulting from the alerting, orienting or working memory components of the task. The absence of modulation of pain and SCR by the orienting and working-memory conditions is due to the variation between trial conditions dependant on direction of attention (towards and away from pain location) (see Supplementary Figures S3 and S4).

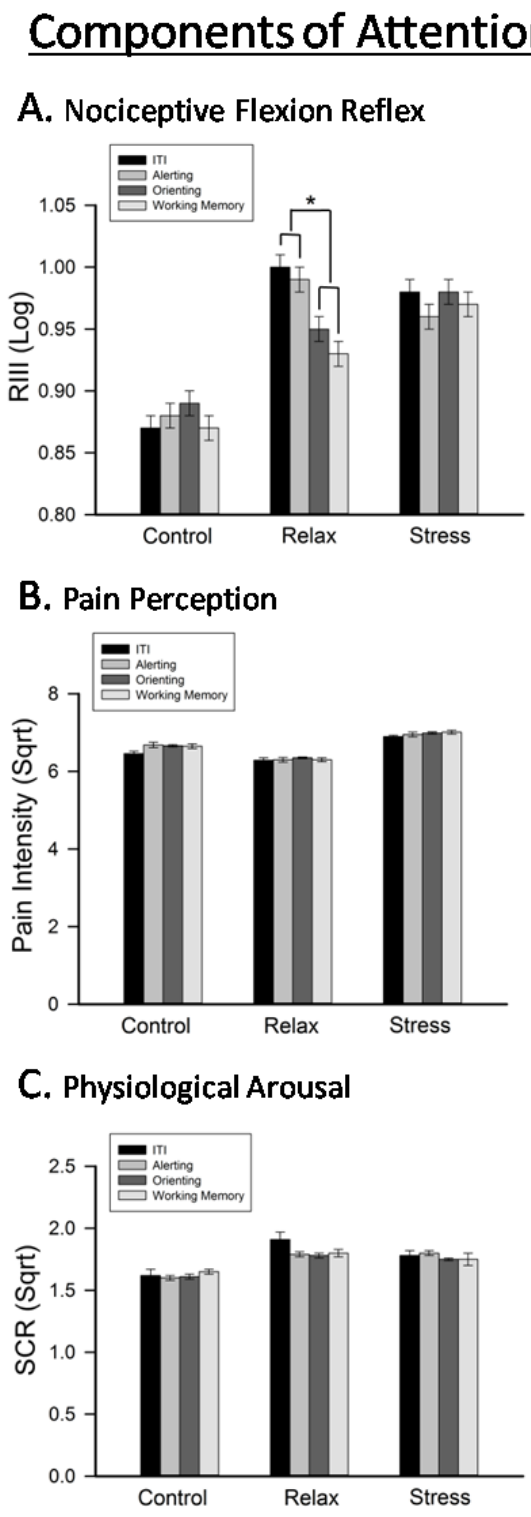

Figure 3. **Orienting and working-memory yielded a significant decrease in NFR (A) in the relax group only.** Components of attention did not produce significant modulation of pain intensity (B) and physiological arousal (C). Error bars represent SEM adjusted to reflect within-subject variance (see Cousineau, 2005). *(p<0.001)

Direction of Attention and Attention Process

The comparison of the orienting and working-memory conditions considering the direction of attention demonstrated additional effects. There was a significant interaction between the direction of attention and stress group on RIII reflex amplitude (interaction: $F(6,78)=2.9$, $p=0.01$). Decomposition of the interaction revealed that there was a significant main effect of direction for the relaxation group ($F(1.8,16.0)=8.6$, $p=0.004$), but not the stress or control groups (p's > 0.05) (Fig.4A). This is consistent with the above results showing that stress inhibits the attentional modulation of the RIII (see Supplementary Figure S5). In the low-stress group, there was significant *facilitation* of the RIII for visual ($p=0.003$) versus vibratory ipsilateral (i.e. towards pain), whereas there was no difference between vibratory contralateral (away from pain) and vibratory ipsilateral (toward pain). The effect of additional executive processing between orienting and the working-memory phase (ISI) tended to decrease further the RIII reflex amplitude ($F(1,26)=3.49$, $p=0.07$) (Fig.3A).

Analysis of pain ratings revealed a different pattern of modulation. There was no interaction between stress and direction of attention or attention process (orienting or working memory) on pain intensity ratings. There was, however, a significant main effect of the direction of attention on pain intensity ($F(2.2,57.5)=3.3$, $p=0.04$) (Fig.4B). Pain intensity ratings were significantly higher when orienting towards the pain location (vibratory ipsi.) compared to towards a visual target (visual) or a somatosensory target away from the pain (vibratory contra.). Pain intensity was not significantly when directing attention towards the location of the painful stimulus (vibratory ipsi.) compared to dividing attention among all targets (divided attention). These effects are in sharp contrast with those of the RIII where facilitation was observed mainly when attention was directed towards the visual in the relaxation group only.

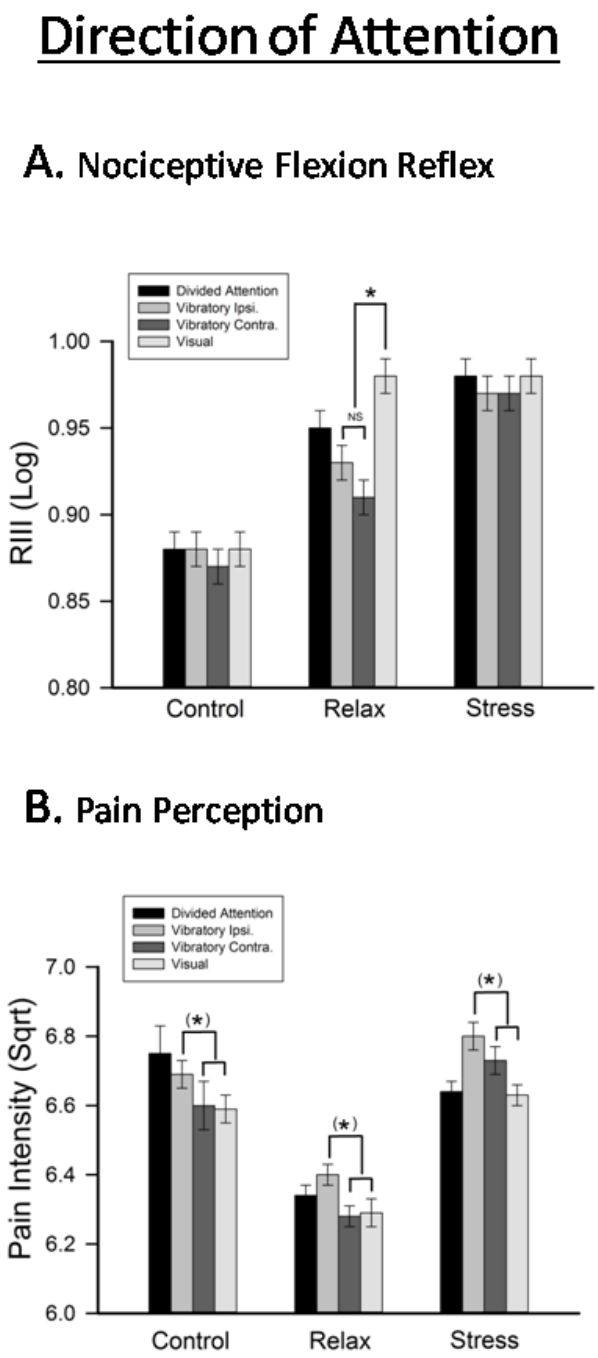

Figure 4. **Direction of attention yielded a modality effect for NFR in the relax group only (A) and a spatial effect for pain intensity (B).** A) NFR. In the relax group, visual attention facilitated whereas vibratory contralateral attention suppressed the RIII compared to vibratory ipsilateral attention. *(p<0.001). B) Pain Perception. Visual and vibratory contralateral attention (i.e. attention away from the location of the shock) reduced pain intensity compared to vibratory ipsilateral attention (i.e. attention towards the location of the shock). (*)(p<0.05). Note analysis of pain intensity revealed no interaction effect between direction and group, therefore (*) represents significance of planned comparisons for overall effect of direction. Error bars represent SEM adjusted to reflect within-subject variance (see Cousineau, 2005).

The pattern of modulation by direction of attention and attention processes also differed for skin conductance response. SCR was significantly modulated by attention and this was dependent on the direction of attention (Direction x Attention Interaction: $F(3,72)=4.4$, $p=0.007$) but not group. Within the orienting phase, SCR was higher when orienting towards visual stimuli (visual) compared to toward the location of shock (vibratory ipsilateral) (Fig.5). The vibratory ipsilateral and contralateral conditions (toward and away from the location of the shock) were not significantly different. In contrast, during the working-memory phase, SCR was lower when orienting toward the location of the shock (vibratory ipsilateral) compared to away from the shock in the vibratory condition (vibratory contralateral) (Fig.5).

Examining the effects of the direction of attention and attention process by comparing across trial conditions, these results show a dissociation between the modulatory effect of orienting on the RIII reflex and pain. Additionally, pain was not modulated by recruitment of working memory whereas this higher order processing tended toward a depression of the RIII reflex. Finally, skin conductance responses demonstrated a modality effect during the orienting phase and a spatial effect during the working-memory phase. Together, these results demonstrate that the direction of attention and attention processes have different modulatory effects at different levels of pain processing i.e. subjective pain perception, nociceptive flexion reflex and physiological arousal.

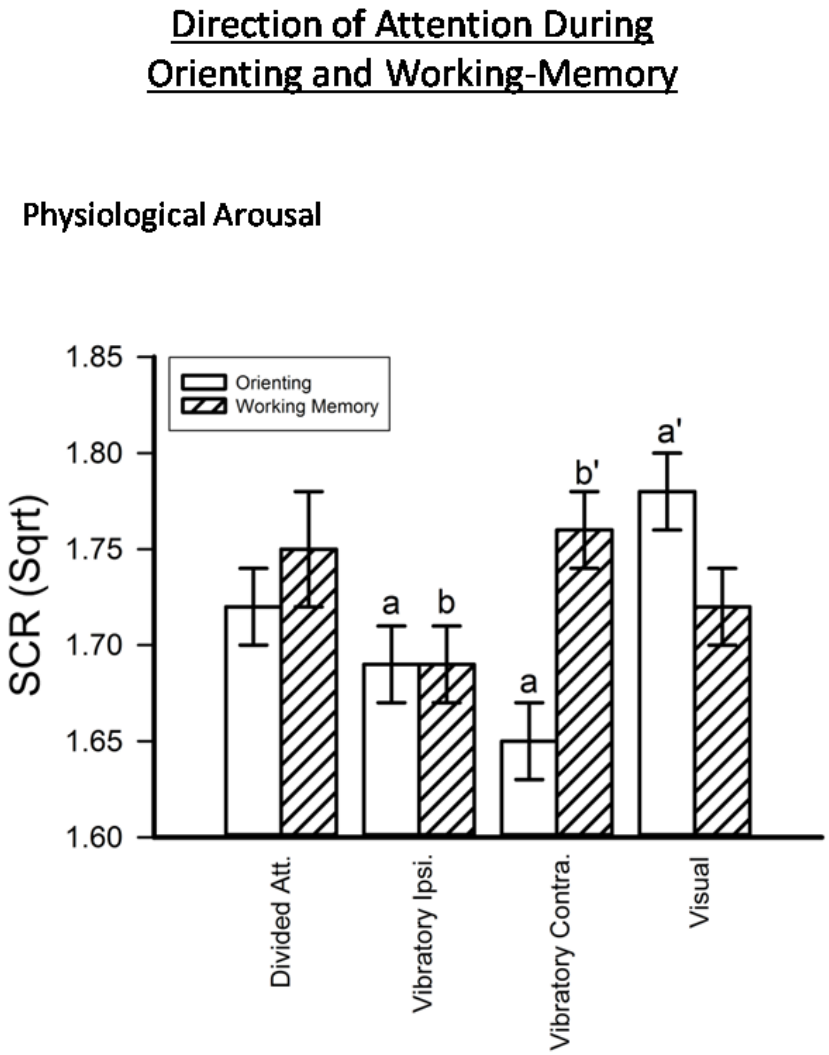

Figure 5. **Direction of attention yielded a modality effect during orienting and a spatial effect during working-memory.** Modality effect during orienting is shown by an increase in SCR when attending to the visual stiumulus compared to somatosensory stimuli (a' vs. a : $p<0.05$). Spatial effect during working-memory is shown by a decrease in SCR when attending to the ipsilateral somatosensory stimuli (b vs. b': $p<0.05$). Error bars represent SEM adjusted to reflect within-subject variance (see Cousineau, 2005).

Discussion

The present study provides a novel conceptual framework with which to consider the seemingly contradictory findings in the literature on the attentional modulation of the RIII and pain and highlights some of the factors possibly contributing to the disparities across studies. Our results demonstrate that the modulation of spinal nociceptive responses and pain by cognitive and affective processes is a complex integration of the effects of stress, the individual influence of each component of attention, and the location and modality of attentional stimuli. Furthermore, while the effects of some factors are facilitatory, others are inhibitory. Moreover, the influence of these elements is different on the RIII reflex and pain, adding to the complexity of attentional modulation of nociception and pain (Table 2). We suggest that the results generated by our novel approach integrate and unify the current literature.

The interaction and dissociation of attention- and stress- mediated modulation of nociception

The current literature on the modulation of the RIII reflex by attention consistently fails to consider stress as a confounding factor in studies using demanding tasks to direct attention away from noxious stimuli. Here, we clearly demonstrate an interaction between attention- and stress-mediated modulation of nociceptive responses and show that higher levels of stress inhibit the attentional modulation of the RIII which was found only in the relaxation group. Furthermore, our results show a dissociation of the effects of attention and stress on spinal nociceptive transmission. By varying levels of stress across groups and engaging different networks of attention processing, our results reveal that supraspinal

Table 2. Effects of Attention and Stress on Pain-Related Responses

	Effect of Stress	Global Task Effect	Alerting	Orienting		Working Memory	
	(Pre- vs. Post-stress manipulation)	(Task vs. Baseline)	(vs. ITI)	Modality[a] (Visual vs. Somato.)	Spatial[b] (Contra vs. Ipsi)	Modality[a] (Visual vs. Somato.)	Spatial[b,c] (Contra vs. Ipsi)
Pain	↓	–	–	–	↓[b]	–	↓[b]
NFR	n/a	↓	–	↑*	–	↑*	-
Arousal	n/a	–	–	↑	–	–	↓[c]

a. Modality effects reflect changes in shock-evoked responses when attention is directed away from the somatosensory modality / toward the visual modality (i.e. Visual vs. Somato)

b. Spatial effects reflect shock-pain reduction when attention is directed away from the foot receiving the shock / toward the contralateral foot (i.e. Contra vs. Ipsi)

c. Spatial effects reflect reduced shock-evoked arousal responses when working-memory is maintaining somatosensory information from the foot receiving the shock (i.e. Ipsi vs. Contra)

↑↓ indicate an increase or a decrease in the corresponding response relative to the control condition at $p<.05$

* This effect is suppressed by stress (i.e. only observed in the relaxation group)

modulation of nociception by attention is separate from the influence of stress, suggesting that these processes are subserved by distinct neural mechanisms.

Effects of different components of attention on supraspinal modulation of nociception and pain

Previous studies have demonstrated that attention has a powerful modulatory effect on nociception and pain, however, this literature is full of seemingly contradictory results on the exact nature of the influence of attention on these processes, and the underlying neural mechanism supporting these effects remain unclear. In the present study we dissociate the major components of attention, namely alerting, orienting, and executive processing (in this case sensory working memory), and demonstrate that these aspects of attention influence nociception and pain in distinct ways. It is not surprising that the components of attention have different influences on pain processing mechanisms as they are functionally and anatomically discrete components supported by separate neural networks and neurotransmitter systems.

Alerting

In the present study, comparison of the baseline condition to the task (effect of task engagement) resulted in a significant decrease in NFR. This general effect of engagement in a task reflects the effect non-specific cognitive resource mobilisation on spinal nociceptive tranmission. Human and animal studies provide evidence that noradrenergic modulation of pain processing associated with activity in the locus coeruleus, considered to be involved in non-specific mobilisation of resources, results in reductions in pain perception and supression of nociceptive reflexes such as the tail-flick reflex in rats (Ramana Reddy & Yaksh, 1980; Jones, 1991; Pertovaara, 2006). Accordingly, our findings of a strong reduction in RIII amplitude between the baseline and task support this interpretation of the results and are

consistent with a noradrenergic-mediated descending inhibition. Although there was no significant difference between the ITI and alerting phase of the attention task on RIII reflex amplitude or pain ratings, the additional recruitment of the alerting network may not have been sufficient to further modulate pain-related responses and therefore failed to provide further supression of the RIII.

Orienting

The orienting component of the attention task had a clear effect on both the NFR and pain ratings. Our results reveal that the influence of attention on pain is spatially-specific but unbiased by the modality of attention-related stimuli. Attentional modulation of nociception however is only modality-specific. The influence of the direction of orienting on nociception and pain is considered in more detail below.

Executive Processing

The working-memory component of attention tended to decrease the NFR between the orienting and working-memory phases of the task and had no significant effect on ratings. The direction of attention during the working-memory phase produced the same spatial effect for pain intensity and modality effect for the NFR as observed during the orienting phase of the task. In conjunction with the findings of a significant effect of orienting on NFR and pain, these results suggest that the analgesic effect of attention and modulation of the RIII rely more clearly on the process of orienting and not due the engagement of executive processing. Previous studies have reported that engaging in a complex task inhibits pain and may involve a descending inhibitory system as evidenced by activations in the periaqueductal grey matter and ventrolateral reticular formation (Bushnell et al., 1999; Bantick et al., 2002; Tracey et al., 2002; Valet et al., 2004; Sprenger et al., 2012). Our results suggest that this hypoalgesic effect

reflects the influence of spatial orienting on pain perception during engagement in the task. Furthermore, the decrease in reflex amplitude during working-memory is consistent with an engagement of a descending inhibitory system and may reflect a non-specific alerting component of the task.

The dissociation of nociception and pain

The RIII reflex has been extensively used in clinical and experimental settings as an objective measure of spinal nociceptive transmission due to numerous reports of its significant correlation with subjective pain ratings. However, recent evidence in the literature suggests a dissociation between nociception and pain perception (e.g. Roy et al., 2011). Our findings of a dissociation between the RIII reflex and pain ratings during engagement in an attention task suggest that supraspinal modulation of pain processes by attention influence spinal nociceptive transmission and pain via different mechanisms.

Attention-related modulation of pain perception: influenced by the location, but not by the modality, of the attended stimulus

Our results suggest that the orienting component of attentional processing is the major contributing factor in the attention-related modulation of pain. Numerous studies have found that distraction from pain produces hypoalgesia. We demonstrate that this phenomenon relies specifically on orienting processes and that this effect is spatially-specific but not influenced by the modality of the distracting stimuli. These properties of pain modulation by attention are made clear from our results of an equivalent significant decrease in pain ratings when

orienting towards either visual or somatosensory stimuli, compared to directing attention toward the site of noxious input.

Attention-related modulation of nociception: influenced by the modality of the attentional stimuli and inhibited by stress

Findings from the present study clearly demonstrate that the modulation of spinal nociceptive transmission by attention is blocked by stress. This supression of nociceptive responses by stress may be due to opïoid-mediated descending inhibition of spinal mechanisms, as it has been demonstrated that opïoid antagonists partially abolish this depression of the NFR in response to stress (Willer & Albe-Fessard, 1980; Willer et al., 1981). In our study, nociception is significantly modulated by attention within the task during the low-stress condition, whereas this attentional modulation of the RIII is suppressed in high-stress or control conditions. One possible interpretation of our results is that the reduction in stress releases spinal nociceptive fibers from a state of tonic inhibition, allowing more subtle effects of attention to be expressed. Complementarily, the low-stress state induced by the experimental manipulation may reflect a normal resting state while higher levels of stress in both control and high-stress groups may reflect an enhanced state of stress due to the experimental setting and stress-inducing manipulation, respectively. The increased thresholds generally observed following familiarization (French et al., 2005) is consistent with the possibility that the typical experimental setting may induce stress leading to a partial suppression of attention-related modulation of nociceptive responding.

In contrast to the exclusively spatially-specific nature of attentional modulation of pain perception, our results reveal that the effect of attention on nociceptive responses is modality-

specific. Orienting *towards* the somatosensory modality produced an *supression* of the RIII reflex, whereas orienting *away* to the visual modality resulted in a *facilitation* of the reflex. This differential effect of stimulus modality on the modulation of spinal nociceptive responses by orienting may be due to the recruitment of descending mechanisms involved in the production of a stronger contrast between competing somatosensory inputs.

Clarifying the Literature: A New Model of Attentional Modulation of Pain-Related Responses

The current literature on the attentional modulation of nociception and pain perception is inconsistent. Where some studies found that attention inhibits NFR (e.g. Bathien & Hugelin, 1969; Edwards et al., 2006; Ruscheweyh et al., 2011), some report a facilitation of the reflex (e.g. McIntyre et al., 2006; Roy et al., 2011), and others show no change (e.g. Dowmann et al., 2001; Terkelsen et al., 2004). Most studies on the influence of attention on pain show a reduction in pain ratings (e.g. Dowmann et al., 2001; Terkelsen et al., 2004; Edwards et al., 2006; McIntyre et al., 2006; Roy et al., 2011; Ruscheweyh et al., 2011), however these results are coupled with differing findings in RIII measures and various associated contradictory interpretations.

The findings from the present study provide a novel framework with which to consider the attentional modulation of pain-related responses (Figure 6) and a means to reconcile the differences in the current literature. First, pain perception is modulated by orienting via a spatial effect of the direction of attention (i.e. orienting away from the site of pain reduces pain perception) and stress reduces pain. Second, spinal nociceptive transmission is modulated by a modality effect of the direction of attention which is inhibited by stress, in addition to an inhibitory effect of a non-specific cognitive resource mobilisation.

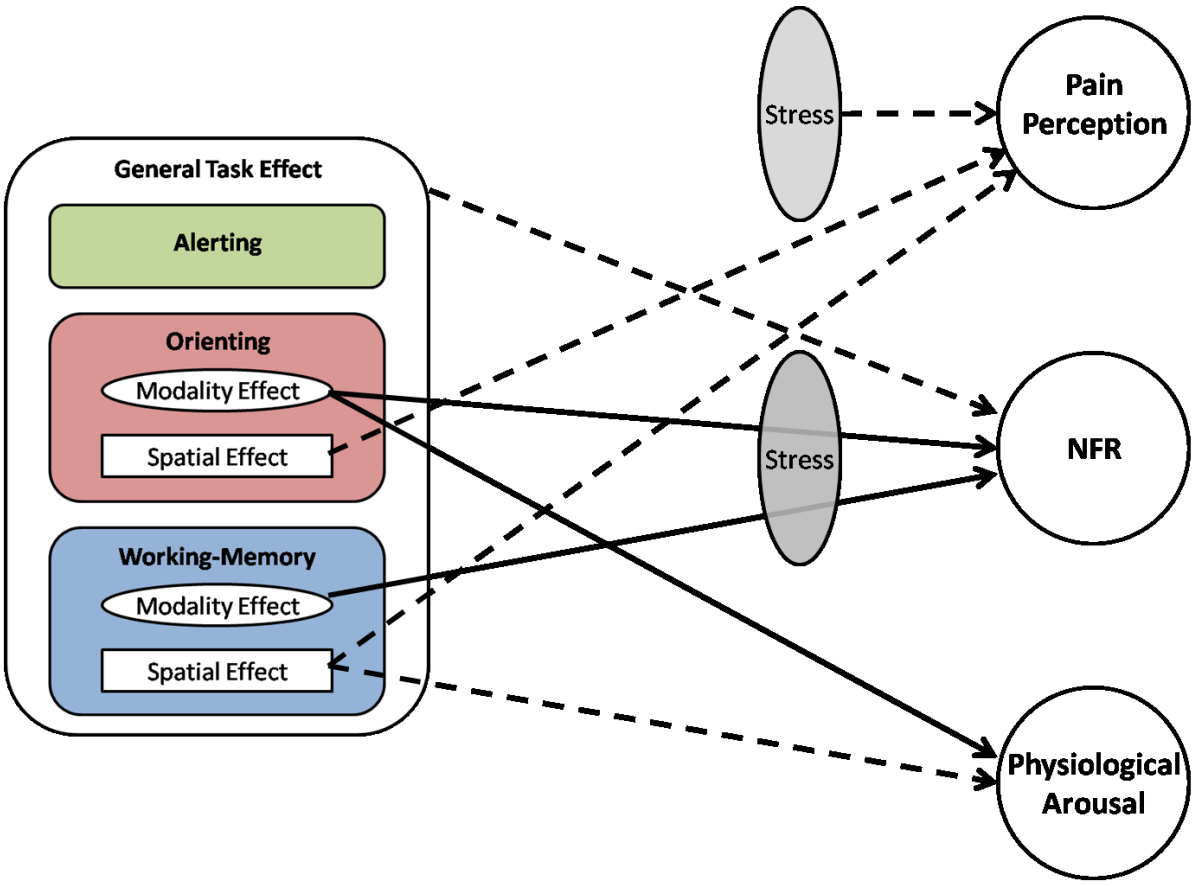

Figure 6. **Effects of attention and stress on pain-related responses.** Pain perception is suppressed by stress and when orienting and working-memory are directed to stimuli away from the site of pain (spatial effect). The NFR is suppressed by the general task effect and facilitated when orienting and working-memory are directed toward a visual stimulus (modality effect); however, this modulatory effect of the NFR is blocked by stress. Physiological arousal is facilitated by directing attention to the visual modality during orienting (modality effect) and is suppressed by directing attention to the somatosensory modality toward the site of pain during working-memory intervals (spatial effect). Solid lines represent facilitation and dashed lines represent suppression.

The apparent contradictions in the literature arise primarily due to the tendency to ignore one or more of the variable effects of stress, modality of stimuli, individual attentional components, and the dissociable influence of these factors on pain perception and NFR. However, re-examination of previous findings with this model clarifies the differing results across studies. Consistent with the predictions of our model on the effects of orienting to the visual modality, Roy et al. (2011) found that within a picture viewing task, viewing neutral images compared to a fixation point decreased pain (spatial effect) and facilitated the RIII (modality effect). Dowmann et al. (2001) found a similar decrease in pain (spatial effect) when orienting toward the visual modality compared to toward pain within a task, but reported no change in RIII (supression of modality effect by stress). In line with predictions of our model on the general effect of engagement in a task, Bathien and Hugelin (1969) showed that engagement in an attention task involving visual stimuli decreased NFR compared to a baseline condition outside of the task (non-specific cognitive resource mobilisation). Ruschewey et al. (2011) found that attention to a finger brushing task (somatosensory away) decreased pain (spatial effect) and RIII measures compared to a baseline condition outside of the task (effect of general task engagement). Although this is not an exhaustive list, the interpretation of the results from previous studies described above illustrates how our framework of attentional modulation of pain processes resolves the differing results across studies.

Conclusion

The present study demonstrates that attentional modulation of pain-related responses is dependent on the components of attention that are recruited, the level of pain processing

engaged (i.e. pain perception, nociception or physiological arousal), and the level of stress induced (for NFR). Our findings show that general task engagement suppresses NFR reflecting the non-specific effect of cognitive resource mobilisation. Additionally, the results reveal that direction of attention during orienting and working-memory generates a spatial effect in pain perception and a contrasting modality effect in NFR, and that this attention-related modulation of the RIII is blocked by stress. These findings highlight the dissociation between attention-related modulation of pain perception and nociception. Moreover, our results show that executive function (i.e. working-memory) does not play a prominent role in attention-related modulation of pain processes. Importantly, our findings demonstrate that non-specific mobilization of cognitive resources, in combination with the direction of attention and modality of attentional stimuli, represent the core elements involved in attention-related modulation of pain processing, and that this modulation of nociception is inhibited by increased stress levels.

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Supplementary Material

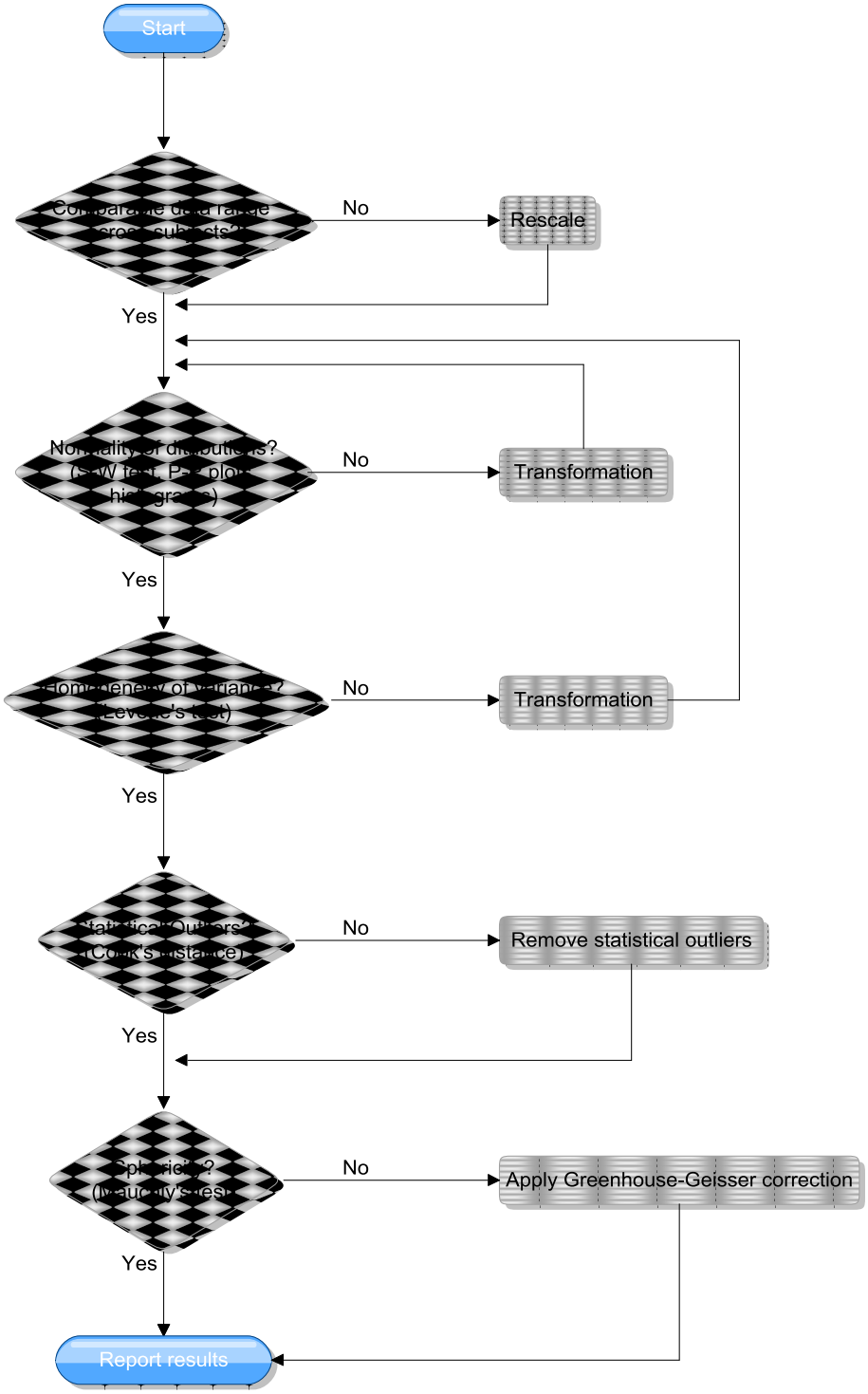

Figure S1. **Pre-treatment of data.** Assessment of data range, normality, homogeneity of variance, statistical outliers, and sphericity were performed on all data prior to statistical analyses. Transformations were selected based on these criteria as indicated.

Table S1. Mean Reaction Times (ms) and SEM of Attention Task Performance

	Somatosensory Left		Somatosensory Right		Visual		Divided Attention					
							Somatosensory Left		Somatosensory Right		Visual	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Easy	1270	66	1298	77	1073	81	-	-	-	-	-	-
Mid-Easy	1217	78	1258	75	1084	98	1273	72	1344	89	1274	124
Mid-Hard	1342	77	1252	68	1195	90	1201	70	1324	88	1167	84
Hard	1257	69	1246	75	1254	102	-	-	-	-	-	-
No change	1456	91	1471	79	1422	89	1447 (88)					

Table S2. Mean Accuracy (Hits and False Alarm Rates) and SEM of Attention Task Performance

	Somatosensory Left		Somatosensory Right		Visual		Divided Attention					
							Somatosensory Left		Somatosensory Right		Visual	
	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM	Mean	SEM
Hits (Easy)	.87	.03	.83	.03	.90	.02	-	-	-	-	-	-
Hits (Mid-Easy)	.84	.03	.79	.04	.91	.03	.80	.05	.71	.04	.77	.04
Hits (Mid-Hard)	.85	.04	.79	.04	.82	.04	.82	.04	.75	.04	.86	.03
Hits (Hard)	.80	.03	.80	.04	.71	.04	-	-	-	-	-	-
False Alarms	.41	.05	.39	.06	.40	.05	.61 (.05)					

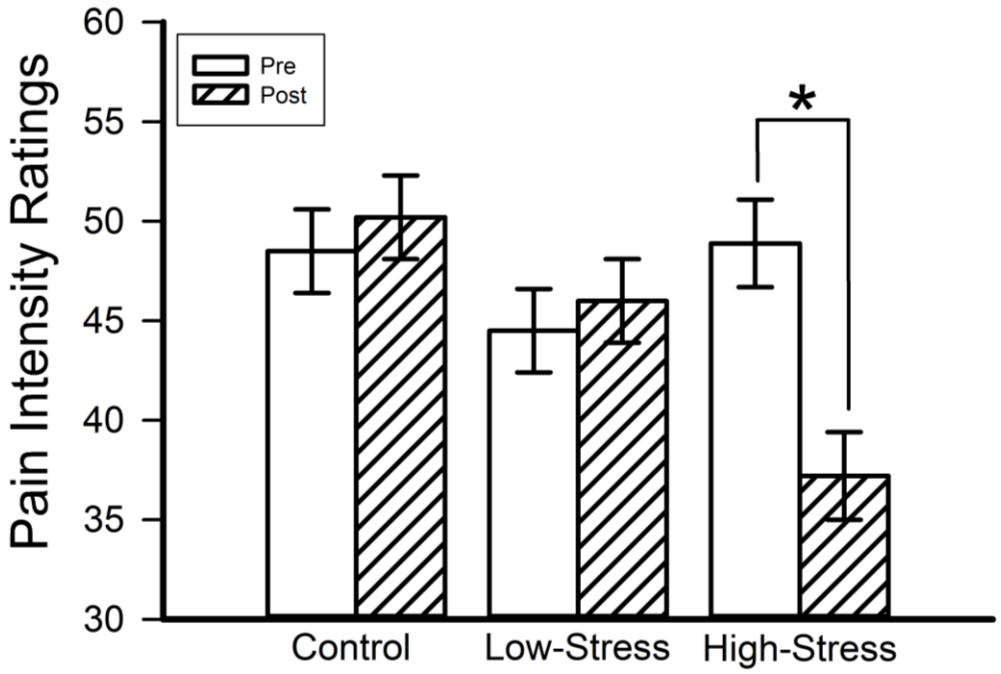

Figure S2. **Pain intensity ratings are reduced by experimental stress manipulation.** Mean pain intensity ratings pre- and post- stress manipulation by group. *(p=0.05)

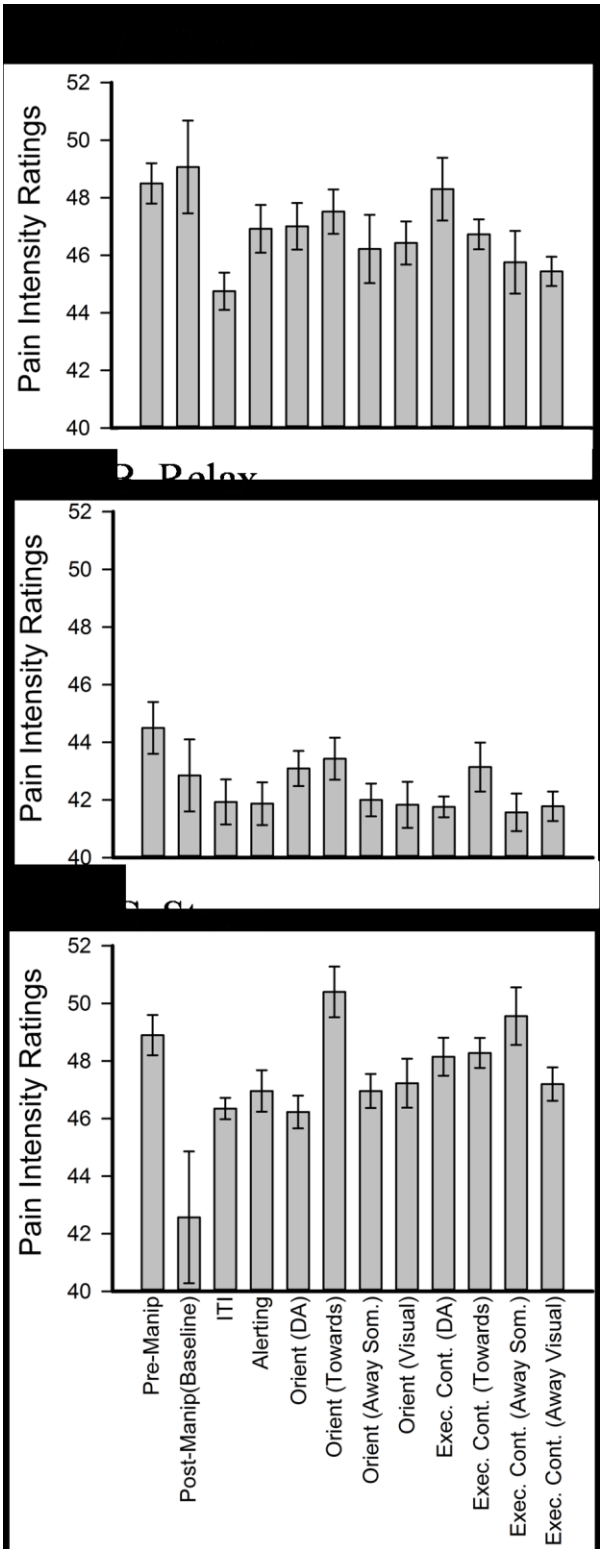

Figure S3. **Means and standard errors of pain intensity ratings for all experimental conditions by group.** (A) Control group; (B) Relaxation group; (C) Stress group. Standard errors were corrected to remove between-subject variability (see Cousineau, 2005).

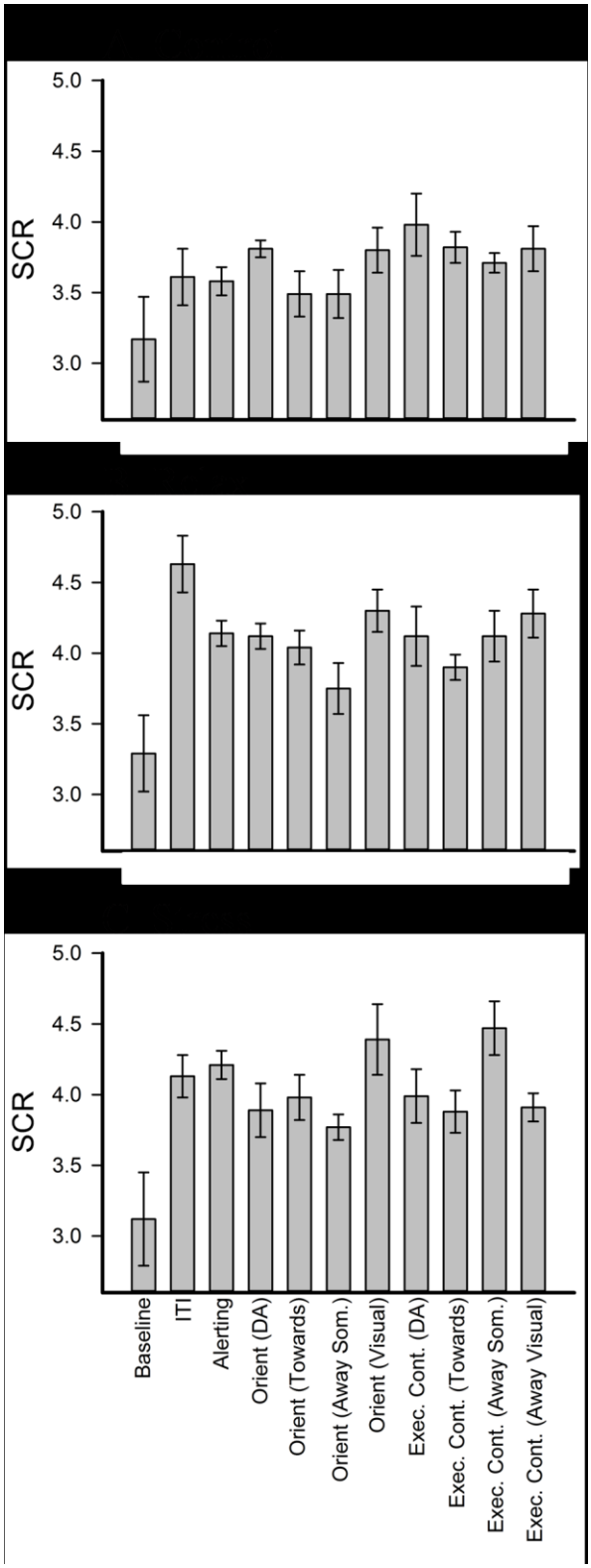

Figure S4. **Means and standard errors of SCR for all experimental conditions by group.** (A) Control group; (B) Relaxation group; (C) Stress group. Standard errors were corrected to remove between-subject variability (see Cousineau, 2005).

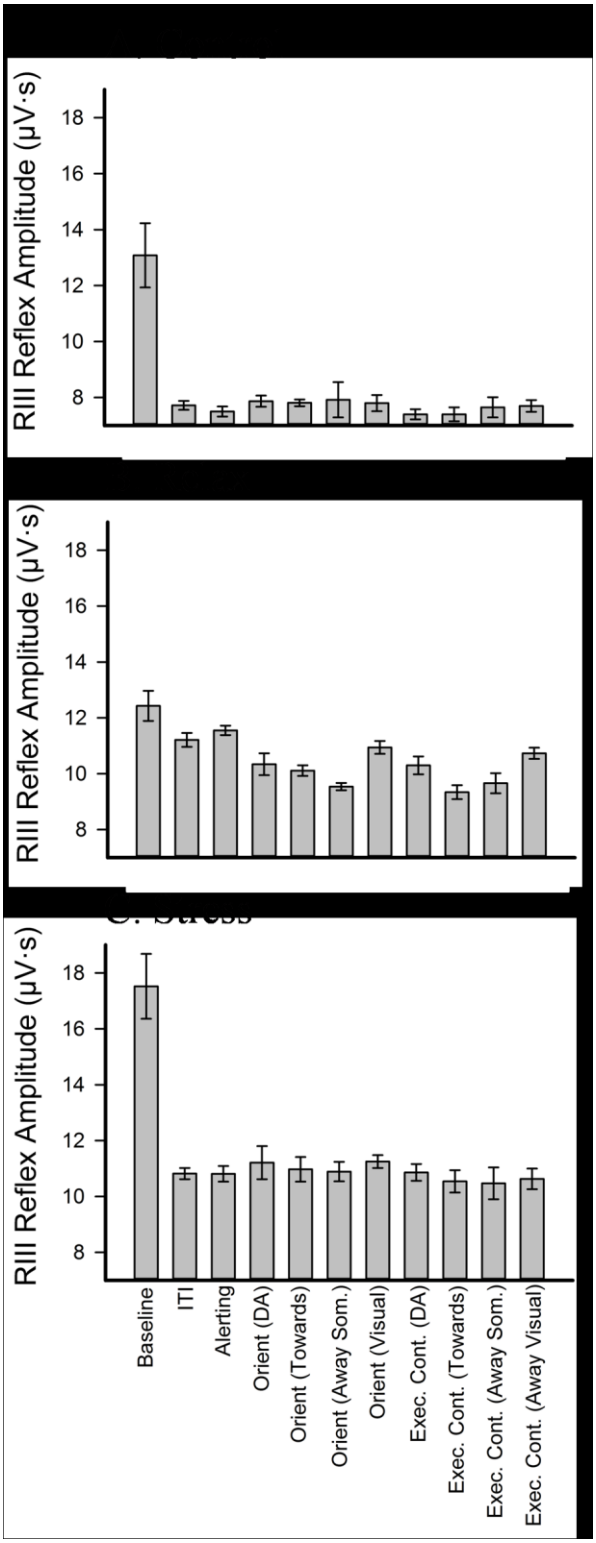

Figure S5. **Means and standard errors of RIII reflex amplitude for all experimental conditions by group.** (A) Control group; (B) Relaxation group; (C) Stress group. Standard errors were corrected to remove between-subject variability (see Cousineau, 2005).

Chapter 3: General Discussion

Chapter 3: General Discussion

The aim of the research in this thesis is to advance our understanding of the spinal and supraspinal mechanisms involved in attentional modulation of pain. A novel framework was developed for investigating the role of the three major attention networks (namely alerting, orienting, and executive control) in pain modulation. Moreover, whether the influence of these components is modality-specific or generalizable was examined by including visual and somatosensory discrimination tasks in the same experiment. In the same study, attention and stress were dissociated with the goal of isolating different cognitive mechanisms involved in the attentional modulation of nociception and pain. The remainder of this text will consist of a summary of the main findings from the present article, followed by the proposal of a new component-based model of attentional modulation of pain processes based on our findings. A detailed review and critical analysis of the current literature and re-evaluation of previous work using this new model will be provided. Finally, possible neural mechanisms underlying the attentional modulation of nociception and pain will be considered.

3.1 Attentional Modulation of the RIII and Pain: New Insights

In the present study, we demonstrate an interaction and dissociation of attention- and stress-mediated modulation of pain processing. To the best of our knowledge, this is the first time that such an interaction and dissociation has been described; thus, a critical reappraisal of the current literature, in relation to our results, is warranted. A second major finding of this thesis is that pain processing appears to be influenced differentially by the individual components of attention, and that the effects of each component on spinal nociceptive

responses and pain perception differ as well. The non-specific effect of the alerting component of the task reduced the RIII reflex but had no effect on pain perception. The orienting component of attention, specifically top-down orienting, appears to represent the major contributing factor in attentional modulation of the NFR and pain. Executive processing did not exhibit a strong influence on either the RIII or pain, suggesting that it is not the mitigating factor in the modulation of pain modulation by attention, as previously thought. However, this may be specific to sensory working-memory and may not be generalized to all executive processing. Finally, the results presented here clearly establish that both the modality and the location of attended stimuli affect the NFR and pain, specifically that attentional modulation of spinal nociceptive transmission is modality-specific whereas the modulation of pain perception is spatially-specific.

The current literature on the attentional modulation of the RIII reflex and pain abounds with incongruity. Some of these disparities within the literature are undoubtedly the result of methodological differences across studies. One important methodological concern arising from our results is the employment of tasks that may significantly increase stress levels and paradigms that fail to isolate the influence of attention from that of stress on pain modulation. Moreover, the current pain literature has largely ignored the multidimensional nature of attention as a process composed of functionally and anatomically dissociable components. Our results emphasize the importance of considering attentional processing in terms of these separate networks and not as a single factor when investigating its influence on pain processing. Additionally, the present findings demonstrate the need to consider both the modality and location of attentional stimuli. Results from the present study suggest the need for a new model of attentional modulation of pain processes with which to re-evaluate the

inconsistencies within the current literature and further our understanding of the underlying neural mechanisms.

3.2 A new model of attentional modulation of nociception and pain

The framework employed in the present study has provided insights into the attentional modulation of nociception and pain that can be organized into a new model that may help further our understanding of the underlying neural mechanisms involved in these processes. This new model includes three tiers: 1-stress inhibits attentional modulation of nociception and reduces pain; 2-the components of attention each influence pain processes differently, and orienting is the major contributing factor; and 3-attentional modulation of pain is spatially-specific whereas attentional modulation of nociception is modality-specific. Because our paradigm did not include an auditory component, the current model does not take into account how orienting/attending to the auditory modality influences the RIII and pain. Hypotheses of how attending toward the auditory system fits within this model will be discussed. Although the current literature appears conflicting, re-evaluation with this new model of attentional modulation of nociception and pain derived from the novel framework elaborated in the present study unifies the seemingly contradictory results into a cohesive unit.

3.3 Reviewing the literature on attentional modulation of nociception and pain: a re-evaluation of the literature

3.3.1 Stress: a confound in the literature

By manipulating stress separately from the attention paradigm, the present study revealed a clear interaction and dissociation of stress- and attention- mediated processes.

Comparing pain ratings before and after the psychological stress manipulation, we found a significant reduction in pain intensity following the experimental manipulation thereby replicating the characteristic stress- induced analgesia that has been shown in previous work on stress modulation of pain (Willer et al., 1981, 1982; Ford & Finn, 2008; Claude et al., 2010; Yilmaz et al., 2010). More importantly, our results show for the first time that stress (as produced in both high-stress and control groups) inhibits attentional modulation of the RIII reflex. These findings from the control group demonstrate that increases in stress levels from exposure to an experimental setting and delayed-discrimination task are sufficient to inhibit modulation of the RIII by attention and accounts for some of the variability across studies. Additionally, by including visual and somatosensory discrimination tasks we show that the modulation of the RIII by attention is modality-specific which emphasizes the need to consider the modality of stimuli employed in attention tasks.

The discordance within the literature on attentional modulation of spinal nociceptive transmission and pain is in part due to stress as a confounding variable. As previously discussed, mental arithmetic tasks are commonly used in studies on stress to elicit a typical stress response (Dickerson & Kemeny, 2004; Ford & Finn, 2008; Yilmaz et al., 2010), however a number of studies investigating the modulation of pain processes by attention employ these same experimental paradigms. Although reliant on attentional processes, the use of mental arithmetic as a distractor introduces an additional confound and obscures interpretation of results from these studies.

Early studies on nociceptive spinal responding examining the effects of several distractor tasks on RIII amplitude in humans report supression of the reflex under conditions of distraction compared to rest (Bathien & Hugelin,1969; Bathien, 1971; Bathien & Morin,

1972). One interpretation of these results is that attention may engage a descending inhibitory system that attenuates spinal nociceptive responses. However, the authors report selecting the tasks in these studies in order to elicit certain typical physiological responses including increased HR and RR, indexes of increased arousal and stress. Hence it was at least overly speculative to attribute these changes in RIII amplitude directly to attentional processing, since the attentional involvement of the tasks were defined by confounding elements of arousal and stress..

Willer et al. (1979) reported an inhibitory effect of attention on both the RIII and pain ratings and an opposing facilitation of these measures in response to stress. Although this seems to contradict the proposed model, Willer et al. (1979) employed a mental arithmetic task as their attentional manipulation and therefore stress is again a confounding variable. On the other hand, the stress induction method in this study consisted of the anticipation of a strong pain and probably reflects the influence of expectancy and not stress. A growing literature on pain modulation by expectancy, supported by studies on placebo, suggestion, and hypnosis, demonstrates that expectations strongly influence spinal nociceptive responses and pain perception (Koyama et al., 2005; Price et al., 2008; Atlas et al., 2012; Buhle et al., 2012; Johnston et al., 2012). Expectation of increased pain has been shown to increase pain ratings (Lorenz et al., 2005; Keltner et al., 2006). Therefore, the parallel facilitation of the RIII and pain in the "stress" condition of Willer et al. (1979) likely reflects the influence of expectancy. Later work by this same lab, found that progressive stress induction by an alternate method to that used in their previous work resulted in a parallel increase in HR and RR coupled with reduced pain ratings and a depression of the RIII reflex (Willer Albe-Fessard, 1980; Willer et al., 1981; Willer & Ernst 1986a, 1986b). These results are in agreement with other studies on

the modulation of pain processes by stress (reviewed by Butler & Finn, 2009) and provide further support for the above interpretation of the findings.

Other studies that used mental arithmetic as a distractor found different results. Some studies report reductions in pain ratings coupled with a facilitation of the NFR, reflected by reduced reflex threshold (Edwards et al., 2006) and increased RIII reflex amplitude (McIntyre et al., 2006), during performance of a paced auditory serial addition task (PASAT), compared to rest. On the other hand, Terkelson et al. (2004) found that performance of the PASAT decreased pain ratings compared to rest, but did not significantly modulate the RIII. Careful examination of these studies reveals several important methodological differences. First, earlier studies by Bathien & Hugelin (1969), Bathien (1971), Bathien & Morin (1972) and Willer et al. (1979) presented numbers for the mental arithmetic task visually whereas the PASAT presents numbers aurally. Our model proposes that attentional modulation of the RIII reflex is modality-specific whereas the modulation of pain is spatially-specific. In line with this, these studies consistently found reductions in pain ratings when attention was oriented away from pain, but results of the effects on the RIII vary considerably across studies. Second, according to the proposed model, attentional modulation of the RIII is inhibited by stress, however this model could not consider stimuli presented to the auditory modality and it is possible that there may be differences in how stress affects modulation of the NFR by auditory attention. Third, disparities between studies may reflect differences in stimulation intensity used. McIntyre et al. (2006) employed a stimulation intensity at threshold whereas Terkelson et al. (2004) selected 1.5 times the reflex threshold. This higher intensity may explain the absence of NFR modulation reported by Terkelson et al. (2004) since the RIII reflex is less susceptible to modulation above certain stimulation levels. Additionally, although these

studies all used mental arithmetic tasks, slight variations between tasks may be sufficient to result in the difference between engaging a stress response or not. For example, the PASAT used by Terkleson et al. (2004) required addition of numbers presented every 2.4s, where as the PASAT employed by Edwards et al. (2006) and McIntyre et al. (2006) involved number presentation every 3.5s, a less speeded, and potentially, less stressful task. Overall, the absence of a control for stress as a confounding variable makes interpretation of these findings difficult, however the proposed model suggests a meaningful and systematic explanation for the inconsistencies.

3.3.2. Components of attention

By decomposing a delayed-discrimination task into the major components of attention, the present study demonstrates that alerting, orienting, and executive processing each modulate pain processes differently. Our results reveal that alerting inhibits both nociception and pain. Taken together with findings from work on noradrenergic pain modulation (for review see Pertovaara, 2006) and the literature on the neurological basis of the alerting network (see general introduction section 1.3.1), it is proposed that the modulation of pain processes by alerting is dependent on the noradrenergic neurotransmitter system and that supression of spinal nociceptive responses is accomplished via a noradrenergic-mediated descending inhibitory system. Additionally, executive processing, specifically sensory working-memory, resulted in a tendency toward an supression of the RIII reflex but had no effect on pain ratings. These findings suggest that the reductions in pain reported during performance of the attention tasks probably do not reflect the influence of executive processing but are more likely mediated by orienting away from noxious stimuli. Moreover, by including both visual and somatosensory conditions, our findings demonstrate that

modulation of pain by orienting is spatially-specific whereas modulation of nociception is modality-specific. The most pronounced modulatory effect of attention on nociception and pain was produced by the orienting component; the details of the influence of orienting on pain processing are discussed below.

3.3.3 Spatially-specific nature of pain

The proposed model posits that orienting away from the site of painful stimuli reduces pain and orienting toward the location of noxious inputs increases pain, whereas RIII reflex modulation is dependent only on the modality of the attended stimuli and increases when orienting toward the nociceptive modality. The studies on attentional modulation of the RIII and pain discussed until this point have found reductions in pain ratings when orienting away from the site of painful electrical stimulation. Additional studies on modulation of the RIII and pain by attention also report reductions in pain ratings when attention is directed away from shocks (Ladouceur et al., 2012; Ruscheweyh et al., 2011; Roy et al., 2011; Dowman et al., 2001; Edwards et al., 2007). Furthermore, reductions in pain were reported by studies that exclusively examined the influence of attention on pain ratings (Davis et al., 1997; Peyron et al., 1999; Petrovic et al., 2000; Frankenstein et al., 2001; Bantick et al., 2002; Nakamura et al., 2002; Valet et al., 2004; Dimitri M L Van Ryckeghem et al., 2011).

Evidence for increased pain, when directing attention toward noxious stimuli, is comparatively less common in the literature. Ruscheweyh et al. (2011) investigated the effect of directing attention to pain on RIII amplitude and pain ratings. Participants were instructed to concentrate on the unpleasantness of the shock. In this experiment, although subjects are orienting to the painful stimuli, there is a potential confound of emotion due to explicit directions to focus on the negative valence of the stimuli. Several studies have demonstrated

that emotion influences both the NFR and pain (Roy et al. 2009, 2011; Rhudy et al., 2005, 2006, 2007). Typically, positive valence reduces and negative valence increases pain and these effects are sometimes coupled with parallel changes in RIII amplitude. Therefore, it is difficult to attribute the findings of Ruscheweyh et al. (2011) directly to orienting towards pain and not emotional modulation.

Terkelson et al. (2004) did not find any effect of directing attention towards the site of noxious stimuli on the RIII reflex or pain. In this study, the "attention towards pain" condition was accomplished by having participants rate pain immediately following the shock, whereas in the baseline condition participants rated pain only at the end of the block of stimuli. The authors may have underestimated the level of attention towards pain in the control condition which also requires subjects to attend to the noxious stimuli in order to perform the delayed-rating task. Because attention was directed towards the pain in both conditions and pain ratings were required in both conditions, the lack of significant attention-related modulation of the RIII or pain is not unexpected.

Ladouceur et al. (2012) recently conducted a study in which the direction of attention was manipulated within a counterstimulation paradigm. The results demonstrated that, during counterstimulation, pain was higher when attention was directed to shock pain compared to when attention was directed to either noxious or innocuous counterstimulation. The RIII reflex was inhibited during innocuous counterstimulation compared to baseline, however there was no additional supression of the reflex was when subjects oriented towards non-painful thermal stimuli compared to orienting towards painful shocks. These findings show that supression of the RIII by orienting away from pain toward the somatosensory modality and depression of the reflex by counterstimulation are not summative and may suggest that these processes rely

on the same neural mechanisms. Additional studies examining the effects of attending towards painful stimuli on pain ratings also report increased pain when orienting toward noxious inputs (Levine et al., 1982; Miron et al., 1989; Villemure & Bushnell, 2002; Quevedo & Coghill, 2007) and provide further evidence that is consistent with the proposed model.

3.3.4 Modality-specific nature of the RIII

The new model of attentional modulation of nociception and pain elaborated from results of the present work proposes that the RIII reflex is unbiased by location and specific to the modality of attended stimuli. More specifically, directing attention to the visual modality facilitates whereas orienting to the somatosensory modality inhibits nociceptive responding. Although the effects of attending to the auditory modality on the NFR could not be included in this model, hypotheses based on the current literature will be discussed. The proposed model, supported by findings of previous studies, explains some of the variability in the literature.

Bathien & Morin et al. (1972) reported that performance of a mental arithmetic task resulted in supression of the RIII; on the other hand, performance of a visual search task (identifying differences between images) produced significant facilitation of the reflex. The authors interpreted these results as reflecting the differential modulation of intensive (math) versus selective attention (visual search). Results from more recent work, such as Ruscheweyh et al. (2011), demonstrate a supression of the RIII during a selective attention task and therefore does not support this rationale. However, the findings of Bathien & Morin et al. (1972) of increased RIII reflex amplitude during engagement in a visual search task can be easily explained by the proposed model that orienting/attending to the visual modality results in a facilitation of spinal nociceptive responses. Findings from Roy et al. (2011) that viewing

neutral images as compared to a fixation point resulted in a reduction in pain ratings and opposite facilitation of the RIII reflex provide additional support for this model.

The proposed model states that orienting to the somatosensory modality depresses spinal nociceptive responses. Ruscheweyh et al. (2011) examined the effects of spatial discrimination of brush stimuli on RIII reflex amplitude and pain ratings. The task involved attending to an irregular pattern and frequency of brushing to all five fingers and counting only the stimuli applied to the index and middle fingers while looking in the opposite direction. This task, which oriented attention away from the site of painful stimulation and towards innocuous somatosensory stimuli, resulted in supression of the RIII reflex and reduced pain ratings, providing support for the model.

Some studies that do not directly investigate attention provide further insight into the attentional modulation of the NFR and pain. Emery et al. (2008) conducted a study examining the impact of progressive muscle relaxation (PMR) on the NFR and pain. The protocol in this study involves directing attention away from noxious stimuli and toward the somatosensory modality and hence can be considered as a distraction manipulation. They found that the RIII reflex *threshold* increased in the PMR group compared to baseline, indicating supression of the NFR, whereas no significant difference was found in controls. The possibility remains that these results are engendered by differences in overall relaxation/stress related to the experimental manipulation. However subjective stress ratings decreased significantly in both the PMR and control groups, making this interpretation unlikely. These results are consistent with the proposed model according to which orienting to the somatosensory modality depresses spinal nociceptive responses.

The model proposed above could not include how attending toward the auditory modality influences the RIII and pain. However several studies provide insight into how auditory attention may be incorporated into the model. Although it is difficult to disentangle the effect of attention from that of stress in these experiments, several studies that employed the PASAT, a mental arithmetic task that presents numbers aurally, report reductions in pain (Edwards et al., 2006; McIntyre et al., 2006; Terkelson et al., 2004) and facilitation of (Edwards et al., 2006; McIntyre et al., 2006) or no change in (Terkelson et al., 2004) the RIII reflex. As previously discussed, the absence of reflex modulation by Terkelson et al. (2004) might reflect the use of higher stimulation intensities or the effects of high stress levels. These findings seem to suggest that orienting/attending toward the auditory modality reduces pain ratings but produces a facilitation of nociceptive responses that may or may not be inhibited by stress. In line with this, several studies have reported reductions in pain intensity ratings during performance of an auditory task compared to attending to pain (Dunckley et al., 2007; Boyle et al., 2008; Silvestrini et al., 2011; Van Ryckeghem et al., 2013). Van Ryckeghem et al. (2013) recently found that orienting towards auditory stimuli away from the location of pain compared to auditory stimuli near the site of pain resulted in decreases in pain ratings. These findings fit with the proposed model that postulates that attentional modulation of pain is spatially-specific. Additionally, Van Ryckeghem et al. (2013) compared orienting to auditory stimuli versus innocuous vibrotactile stimuli and found a reduction in pain ratings when orienting to the auditory modality. These findings suggest that attentional modulation of pain is not only spatially-specific but also modality specific. However, it remains possible that the auditory and somatosensory stimuli presented in this experiment were not of equivalent saliency and that the reduction in pain during orienting to auditory as compared to

somatosensory were saliency driven and not a result of modality. Taken together, orienting/attending to the auditory modality seems to produce a facilitation of nociceptive responses and reductions in pain which are due to orienting attention away from pain.

3.4 Neural mechanisms of attentional modulation of pain

The neural mechanisms underlying the modulation of pain processes by stress have been demonstrated by previous authors to be dependent on an opïoid-mediated descending inhibitory system (Willer & Albe-Fessard, 1980; Willer et al., 1982; Ford & Finn, 2008; Butler & Finn, 2009; Claude et al., 2010; Yilmaz et al., 2010). Results from the present study are consistent with this concept and further suggest that attentional modulation of nociception and pain are reliant on distinct neural mechanisms that interact with this system. Future studies employing opïoid antagonists during performance of an attention task may provide further evidence that attentional modulation of pain is independent of opïoidergic system.

The literature on the neurobiology of the components of attention demonstrates that the alerting network is dependent on a noradrenergic neurotransmitter system mediated by the LC (see general introduction section 1.3.1). Several human and animal studies have investigated the influence of this system on pain by pharmacological manipulations and direct stimulation of the LC and show that increased NE and activation of the LC produce an inhibition of pain related responses (Ramana Reddy & Yaksh, 1980; Jones, 1991; Pertovaara, 2006). Results from the present study show decreased pain and RIII reflex amplitude during alerting. Taken together, these findings suggest that modulation of pain processes by alerting are consistent with an activation of the noradrenergic neurotransmitter system and that inhibition of nociception is produced by a noradrenergic-mediated descending inhibitory system.

The manipulation of orienting toward different locations and modality of attentional stimuli in the present work provides insight into the possible underlying neural mechanisms. Findings from the present study show that attentional modulation of pain is spatially-specific whereas modulation of spinal nociceptive transmission is modality-specific. This spatial specificity of supraspinal mechanisms may reflect a selection-bias to task relevant inputs and results in a bias toward processing attentional stimuli resulting in the reported reductions in pain. At the supraspinal level, noxious stimulus processing is reduced in order to support processing of attentional stimuli during orienting away from pain and therefore perception of painful stimuli is diminished. The modality-specific nature of attentional modulation of spinal nociceptive responding also reflects the prioritizing of stimulus processing, but here at the spinal level. The supression of the RIII reflex observed during orienting to the somatosensory modality may be dependent on a gate-control system as seen during innocuous counterstimulation. Ladouceur et al. (2012) demonstrated that counterstimulation resulted in a decrease in RIII amplitude compared to baseline, however no additional inhibitory effect on the RIII reflex was observed during orienting toward innocuous counterstimulation compared to orienting toward the shocks. Moreover, this supression is not reported during orienting to the visual or auditory modalities. In contrast, facilitation of spinal nociceptive transmission during orienting to the visual and auditory modalities likely reflects a release from a state of tonic inhibition and possibly underlies a protective mechanism that potentiates the withdrawal reflex when attending to a different modality. Additionally, the cholinergic system is likely involved in the modulation of pain processes underlying the orienting component of attention. Top-down orienting has been shown to depend on the cholinergic system (see general introduction section 1.3.1). However, cholinergic modulation of pain has not been thoroughly

investigated, and pharmacological manipulation of this system reflecting orienting processes to different locations and/or sensory modalities is currently not possible.

Executive control processes tended toward a supression of the RIII reflex, suggesting that this depression is subserved by a descending inhibitory system. In line with the dependence of executive processing on prefrontal regions, previous studies have demonstrated increased activity in the PFC in conjunction with increases in the PAG during performance of an attention task (Bushnell et al., 1999; Bantick et al., 2002; Tracey et al., 2002; Valet et al., 2004). These findings suggest that executive processing engages the PFC which initiates a descending inhibitory system mediated by the PAG. However, the possibility remains that this may reflect stress-mediated modulation of pain processes as these studies do not isolate attention from stress.

The present study proposes a new perspective with which to consider the attentional modulation of nociception and pain. The results presented above clearly demonstrate 1) the dissociation and interaction of attention- and stress-mediated modulation of pain processes, 2) the role of the individual components of attention in the modulation of pain processing, and 3) the modality- and spatially-specific nature of attentional modulation of nociception and pain, respectively. The proposed model, based on these findings, offers a systematic approach with which to resolve the inconsistencies in the current literature and provides insight into possible neural mechanisms underlying attentional modulation of nociception and pain.

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