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Chewing Gum Analgesia: a Test of the Effects of Physiological Stimuli on Pain Intensity and Affective Responses to Routine Painful Procedures in Children

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A thesis submitted to the faculty of Graduate Studies and Research in partial fulfillment of the requirements of the degree of Master of Science

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Abstract

The aim of this randomized, controlled trial was to test whether sweet taste and chewing modify self-report of pain intensity and negative affect caused by blood-draws and vaccination in children. Subjects were recruited (age mean±SD; 9.82±0.8 years) from schools (n=115) and a hospital (n=101). Subjects were assigned to Control, Sweet, Chew or Sweet+chew interventions. Pain intensity was rated on the Coloured Analogue Scale (CAS) and affective quality on the Faces Pain Scale (FPS).

In school and hospital settings a Sex by Sweet by Chew interaction was seen on CAS (p=0.29; p<0.01) and FPS (p<0.05; p<0.05) respectively. A consistent pattern was seen in which chewing reduced and sweet taste increased pain ratings in boys. The opposite effect was seen in girls. When sex was not considered no significant differences between groups were seen.

Sweet taste and chewing appear not to have useful analgesic effects. Sex must be considered in future investigations.
Cette étude, contrôlée par randomization, avait pour but de déterminer si le goût sucré et la mastication de gomme à mâcher affectent l’expérience douloureuse durant les immunisations ou lors d’un prélèvement sanguin.

Les sujets ont été recrutés (âge moyen±ET: 9.82±0.8 ans) dans deux écoles (n=115) et un hôpital (n=101) et furent assignés à un des quatre groupes suivants: Contrôle, Goût Sucré, Mastication ou Goût Sucré+mastication. Les sujets devaient évaluer combien forte et désagréable était la douleur en se servant d’une échelle qui utilise des couleurs, la Coloured Analogue Scale (CAS), et une autre basée sur des dessins de visages, Faces Pain Scale (FPS).

Dans les écoles, ainsi que dans l’hôpital, une interaction Sexe par Goût Sucré par Mastication fut observée sur la CAS (p=0.29; p<0.01) et la FPS (p<0.05; p<0.05).

Cette étude à constamment menée à l’observation que, la mastication réduit et le goût sucré augmente les évaluations de douleur chez les garçons. Par contre, l’effet inverse était observé chez les filles. De plus, lorsque le sexe des sujets n’était pas considéré dans l’analyse, aucune différence ne fut décelée entre les groupes.

En conclusion le gout sucré et la mastication ne semblent pas avoir d’effets analgésiques et par ailleurs, le sexe des sujets doit être considéré dans les prochaines études.
Chapter 1: Literature Review

Introduction

Working definition of acute pain

Pain in all its forms is a challenging concept to define and study. The present study is limited to examining acute pain, which is neither chronic, nor progressive, nor of neuropathic origin. Pain has been defined by the IASP Subcommittee on Taxonomy as an unpleasant sensory and emotional experience associated with real or potential tissue damage (or described in terms of such damage) (Merskey et al., 1979). This definition does not tie pain to a stimulus, as was done traditionally, and identifies pain as distinct from nociception, the response of pain-reception neurons.

Two pioneers of pain research in psychology, R. Melzack and P. D. Wall, considered that pain is best described “in terms of a multidimensional space comprising several sensory and affective dimensions” (1983). They argued that this was due to the diversity of pain experiences and the variability of the link between pain and real or threatened tissue damage. Melzack and Katz have since proposed three major psychological dimensions to pain: sensory-discriminative, motivational-affective and cognitive-evaluative (see 1989).

The gate control theory of pain, elaborated by Melzack and Wall, argued that nociception (the response of the pain-reception neurons) was only the first part of the process required for the perception of pain (1965). These authors proposed that cells within the substantia gelatinosa of the spinal cord act as a gate control system (i.e. as modulatory intermediates involving inhibitory interneurons). The gate control system, through pre-synaptic inhibition, could modulate neural transmission from peripheral
receptors to cells transmitting the information to the brain. Descending inputs from brain
stem neurons could also modulate pain through this system (Melzack & Wall, 1965).

Issues of alleviating pain in children

Children undergoing medical procedures have been undermedicated with
analgesics (Barr, 1989). Compared to adults, children undergoing surgery receive less
potent analgesics in lower prescribed and administered doses (Barr, 1989). There is also
a documented lack of intraprocedural analgesia during painful procedures like
circumcision (Barr, 1989). Burned children are undermedicated for pain compared to
adults, even though the consequences of such pain may be particularly severe in children
(e.g. delirium, depression, and PTSD) (Latarjet & Choinere, 1995).

In addition to the humanitarian imperative to treat pain in children,
untreated pain can influence the course of illness or affect future health seeking and
compliance behaviours of patients and their parents. For example, inadequate pain
management in burn care can cause a loss of confidence between the medical team and
patients, leading to problem behaviours by both parties (Latarjet & Choinere, 1995). It
has also been suggested that experiences during hospitalizations may desensitize children
to some fears while creating others (Aho & Erickson, 1985).

Inadequate pain management in children may be the result of inaccurate pain
assessment by medical team members or parents (Manne et al., 1992). Pain and anxiety
from medical procedures are often related in children but vary by procedure. Children
fear needles and the pain they cause (Humphrey et al., 1992). A study of medical fears
found that the most frequently endorsed fears of 7 to 13 year-olds were procedures
involving needles, such as stitches and blood-draws (Aho & Erickson, 1985). However,
pain and anxiety associated with routine minor procedures involving needles are habitually ignored. In neonates, vaccinations and heel stick procedures are consistently done without any attempt to reduce the pain although a number of simple, “natural” interventions such as breast feeding, maternal contact, and sweet solutions placed in the mouth, have all been shown to be effective (Gormally et al., 1996; Gormally et al., 2000) (Blass & Shah, 1995; Barr et al., 1993).

Particularly germane to this thesis, Fradet et al. (1990) examined a sample of 2-6 year olds and a sample of 7-17 year olds having a blood-draw and asked them to rate their pain on self-report scales. Fifty-seven and 53 percent of the samples respectively reported pain from venepuncture in the mild to severe range (1-10). The older sample also rated their distress before the procedure and had a mean rating of 2.8 on 10. Pain intensity, and distress prior to blood-draw, were not insignificant. In one sample of 150 hospitalized children between the ages of 3 and 18, the three most commonly reported painful procedures were needle procedures, venepuncture (blood-draws), IV insertions and injections (Wong & Baker, 1988). On a scale of 0 to 10, mean pain ratings were 2.7 for venepuncture, 2.0 for fingerprick and 2.5 for injections (Wong & Baker, 1988). Similar levels of distress were reported.

There is evidence of a negative impact of minor procedural pain on infants (see Taddio et al., 1997). Pain, such as that caused by circumcision, affects subsequent reactions of infants to pain four to six months later (Taddio et al., 1997). In summary, it appears desirable to treat minor procedural pain in children, such as the pain from needle procedures, by practical and effective means.
Effect of sweet taste on pain response

Sweet taste, in the form of solutions or foods, appears to have analgesic and cry reducing properties. The relevance of the animal literature on sweet taste and pain to humans can best be conceptualized in the following way. The nursing-suckling relationship is specific to mammals. Major and minor aspects of this relationship are conserved across mammalian species. The similarity of the behavioural and functional characteristics of this relationship across mammalian species underlines the direct relevance to humans of studies in the rat (Blass. 1999). Outlined below are studies that examined the effects of sucrose on analgesia.

Sweet tasting solutions placed on the anterior part of the tongue have been shown in various experimental situations to reduce crying in human (Graillon et al., 1997; Smith et al., 1990; Barr et al., 1999) and animal (Blass & Fitzgerald, 1988; Blass et al., 1987) infants. This effect has been demonstrated in infants crying spontaneously or in response to a painful stimulus. Studies in animals have shown that administration of a sweet tasting solution to the anterior portion of the tongue can function as an analgesic (Blass & Fitzgerald, 1988; Blass et al., 1987). Blass, Fitzgerald, and Kehoe (1987) found that sucrose solution, but not water, given orally to 10-day-old rat pups increased their escape latencies from a heated surface (48°C). Intraoral milk infusions also reduce pain behaviours in 10-day-old rat pups (Blass & Fitzgerald, 1988).

The effects of sugar solutions on pain responses have also been examined in human term neonates. Numerous studies have reported that sweet solutions administered to the anterior portion of the tongue reduce responses of neonates to painful procedures
Comparisons of orally administered solutions of 30% glucose and 30% sucrose produced identical analgesic effects, as assessed on a validated behavioural pain measure, in newborns undergoing routine venepuncture blood-draws (Carbajal et al., 1999). This effect was large enough to be detected using a behavioural rating scale, and the two-point difference on a ten-point scale was considered clinically significant by the authors (Carbajal et al., 1999).

Smaller volumes of lower concentrations of sucrose solutions are also effective. As little as 0.1 ml of 14% sucrose solution caused a reduction in crying in newborns undergoing heel-prick blood-draws (Smith et al., 1990; Blass & Hoffmeyer, 1991). Infants who received sucrose solutions were not simply less aware or more sleepy but in fact were increasingly in a calm alert state (Blass & Hoffmeyer, 1991). Blass and Hoffmeyer also found that during circumcision, infants who were given sucrose-dipped pacifiers cried about 50% less than infants receiving nothing and around 25% less than infants who received a pacifier dipped in water (1991).

Barr et al. (1993) have since demonstrated that orally administered sucrose solution can reduce crying to heel prick by 40% in human neonates. In addition, 24% sucrose solution and holding contact (i.e. holding the infant to one’s chest) interact to alter neonates’ reactions to pain. Sweet tasting solution and holding contact alter both behavioural and physiological (i.e. heart rate and vagal tone) reactions of neonates to heel-prick induced pain (Gormally et al., 1996; Gormally et al., 2000).

The analgesic effects of orally administered sweet tasting solutions have also been examined in preterms and in older infants. In preterm infants undergoing heel lancing,
both single and repeated doses of 0.05ml of 24% sucrose solution cause reductions in scores on behavioural and physiological indicators of pain (Johnston et al., 1999). Single doses of sweeter solution (2mL of 50% sucrose wt/vol.) also reduce pain responses to heel lancing in preterm infants (Bucher et al., 1995). These effects have also been observed in older infants (ages 2 to 4 months) whose responses to immunization were reduced by tasting a sucrose solution (Barr et al., 1995).

Sweet taste analgesia has also been studied in older children undergoing the cold-pressor test, an experimental pain task in which the participant places their arm in water kept at a constant cold temperature. The subject's pain threshold is defined as the delay between submersion of their arm in the water and the time at which they first signal that they feel pain. Tolerance is the latency to withdrawal of a subject's arm from the water. One study examined pre-adolescents who were given a sucrose solution while they undertook a 10°C cold-pressor test. The study found that children who held a 24% sucrose solution in their mouths during the test had a 35% prolongation of pain threshold compared to water (Miller et al., 1994). No differences in tolerance or pain intensity ratings were observed however.

Very few studies have examined the effects of sweet taste on pain in adults. One study comparing tolerance to pain caused by an algometer found that ingestion of a sweet food rated palatable (chocolate-chip cookies), but not a neutral (rice cakes) or "unpalatable" (olives) food, increased tolerance to pain, but only in women (Mercer & Holder, 1997).
Effect of rhythmic oral movements on crying and pain

Sucking appears to be analgesic in rats. Rats pups sucking the nipples of anaesthetized dams show increased thresholds for pain and have reduced behavioural responses to painful thermal stimuli (Blass, 1996). Combining such nonnutritive suckling with sweet taste has an even greater analgesic effect (Ren et al., 1997).

The analgesic effect of sucking and chewing in human infants has been evaluated in a small number of studies. Research on newborns undergoing heelstick procedures and circumcision support the potential analgesic effect of non-nutritive sucking of a pacifier. Infants who sucked on a pacifier spent less time fussing and crying during and after a heelstick procedure (Field & Goldson, 1984). Similarly, infants given a pacifier while undergoing circumcision cried 40% less than infants who did not receive a pacifier (Gunnar et al., 1984). Blass and Hoffmeyer also found that sucking a pacifier dipped in 24% sucrose solution or water was more effective in reducing crying during circumcision than no intervention (1991). Infants who received sucrose cried significantly less than did those in either of the other groups.

A recent study by Carbajal et al. (1999) examined neonates undergoing heel prick blood-draws. The authors compared the analgesic effects of sucrose and glucose solutions and found that non-nutritive sucking of a pacifier was more effective than either 30% sucrose or a 30% glucose solution. In addition, they found evidence for a synergistic effect of sucrose and pacifiers. This effect occurred when sucrose and pacifier were administered together and an almost six point median difference in pain evaluation on a ten point behavioural rating scale was found (Carbajal et al., 1999).
Similarly, Blass and Watt found that pacifiers induced analgesia in newborns receiving heel stick, but only when the infants sucked at a rate of over 30 sucks per minute (1999). When sucrose was combined with pacifier administration, analgesia was almost complete (1999).

**Proposed mechanism of sweet taste analgesia**

Evidence that sweet taste analgesia is consistent with opioid mediation

**Opioids**

In order to discuss the possible involvement of an endogenous opioidergic system in sweet taste analgesia a brief overview of opioids is essential.

Opioids are endogenous neural polypeptides, such as enkephalin, that have marked affinity for opioid receptors and that mimic some of the analgesic properties of opiates. Opiates are narcotic preparations, such as heroin and codeine, derived from opium, which induce sleep and alleviate pain. The opiate morphine is the archetypal and most commonly indicated drug for the treatment of serious chronic clinical pain, such as cancer pain (Twycross, 1989). Opiates are classified by their strength (weak or strong) and their receptor site affinities. Most clinically used opiates are mu receptor agonists that, in the spinal cord of rats, exert both pre-synaptic effects on primary afferent C-fibers and post-synaptic effects on dorsal horn nociceptive neurons (Dickenson, 1995). The pre-synaptic actions of mu agonists inhibit release of excitatory neurotransmitters such as glutamate and the tachykinin family of peptides such as substance P. The effects of activation of post-synaptic opioid receptors are more complex to interpret (Dickenson, 1995).
The human opioidergic system is the endogenous mechanism of analgesia through which opioid agonists, such as morphine, exert their effect. Opiates and opioids are effective analgesics, as measured by behavioural indicators in humans and mammals and as assessed by self-report in humans. There is evidence, discussed below, suggesting that the analgesic effect of sweet tasting substances, as shown in the young of various species, may work through modulation of endogenous opioid systems.

The endogenous opioid system has long been known to be involved in the reduction of pain perception (Panksepp et al., 1997). Opioids modulate pain through mechanisms within the spinal cord and brain (Dickenson, 1995). Spinal cord and brain neural pathways underlying such systems can be classified as belonging to either ascending or descending systems of analgesia. "Ascending" and "descending" refers to the direction, in relation to the brain, of projections in the central nervous system (CNS). through which analgesia occurs. Descending, or antinociceptive, analgesia occurs when opioids act directly on the spinal cord or on descending inhibitory systems projecting from the brain stem to the spinal cord (Franklin, 1989). Ascending, or dissociative, analgesia is that (described by clinicians) in which administration of opioids relieve suffering, without a necessary concomitant reduction of nociception (i.e. of the sensory intensity of pain). Some patients in pain report dissociation between pain sensation and affect relating to pain. When treated with opioids such patients will remark that “It hurts but the pain does not bother me” (see Franklin, 1989).

Sweet taste and Opioids

Experiments involving rats offer some direct evidence of opioid involvement in sweet taste analgesia. The analgesic effect of sucrose solution appears to be mediated by
an endogenous opioid system since an opioid antagonist, naltrexone, can attenuate the increase in escape latency from a heated surface due to intraoral sucrose in 10-day-old rat pups (Blass & Fitzgerald, 1988). A similar naltrexone reversible analgesic and calming effect has been demonstrated for milk (Blass & Fitzgerald, 1988). However, in keeping with the complex structure of milk, its effectiveness is probably attributable to a number of mechanisms (Blass, 1999).

Indirect evidence for the possibility that stimuli such as sweet taste may invoke an endogenous opioidergic system comes from clinical populations (Blass & Ciaramitaro, 1994; Barr et al., 1994; Graillon et al., 1997; Blass & Shah, 1995). Specifically, Blass and Ciaramitaro observed that infants born to mothers addicted to methadone, a synthetic form of morphine, and thus born in withdrawal do not calm in response to sucrose solution (1994). Furthermore, in postmature infants (Clifford's syndrome), infants who have high levels of endogenous opioids and thus are assumed to be tolerant to endogenous opioids, sucrose taste is a less effective soother (Smith et al., 1992). Postmature infants require higher concentrations of sucrose solutions to soothe and the calming effect does not persist as long as in term infants (Smith et al., 1992). In postmature infants however, pacifier administration remains effective for soothing suggesting that sweetness and rhythmic oral movements modulate soothing, or analgesia, through independent or parallel endogenous systems (Blass & Ciaramitaro, 1994).

An analgesic effect of food, possibly similar to that seen in infants and children, has been described in human adults. Zmarzty et al. (1997) have found that food, particularly that which is high in fat and low in carbohydrates, reduces pain caused by a cold pressor stimulus. The authors suggest that this effect is a post-ingestive amplification of pre-ingestive orosensory stimulated analgesia since it peaked at 1.5 hours after the
meal. This long after a meal no food taste remains in the mouth and digestive effects are most likely to be in effect. In a later study, they failed to find analgesic effects from ingestion of food when the taste and cognitive components of food ingestion were bypassed by intragastric infusions of carbohydrates or fat (Zmarzty & Read, 1999). Zmarzty et al. therefore argued that endogenous opioids, thought to be released in response to food palatability, are not released by intragastric infusion of food (1999). Their work appears to support a pre-ingestive analgesic effect of food in adults possibly occurring through an endogenous opioidergic mechanism. This analgesic effect may be related to the analgesic effect of sweet taste documented in infants.

A two-phase cry reducing response to sucrose solution in infants has been proposed (Barr & Young, 1999; Barr et al., 1999). This calming response includes a “stimulus bound” phase, resulting from the presence of an oral stimulus, and a subsequent “poststimulus” phase. Stimuli of equal salience to sweet taste, such as quinine (the archetypal bitter taste), can also activate this first phase of soothing in newborns. When compared with quinine, sucrose solution effects in reducing crying lasted longer and were stronger (Graillon et al., 1997). Furthermore, the soothing effects of Aspartame (a non-nutritive sweetener) are almost identical to those of sucrose. This supports the claim that these effects are “sweetness” induced, orally mediated, pre-absorptive and independent of the class of nutrient to which the sweet solutions belong (Barr et al., 1999). The points outlined above support such a distinction as well as the suggestion that the “poststimulus” phase of sweet taste analgesia involves some central changes which may be opioid-dependent. It is this second effect that persists for minutes beyond termination of the oral stimulus. The current study capitalized on the prolonged, or “poststimulus”, effect of
sweet taste analgesia in the design of the experimental groups. described below (see Chapter 2).

Another relevant but unanswered question regarding the mechanism of action of sweet taste analgesia is whether it is a hedonic effect or a sweetness effect. It is unclear whether the pleasantness or rewarding properties (i.e. the hedonicity) of sweet taste can account for its analgesic effects. Sweetness may itself be responsible for analgesia, independent of its pleasurable properties. These two possibilities may not be mutually exclusive and both are consistent with an opioid mediated effect of sweet taste analgesia. In fact, sucrose may be perceived as hedonically positive because the sweet taste itself may cause the release of endogenous opioids (Blass, 1987). The apparent overlap of the neural substrates of analgesia and reward (Franklin, 1989) is consistent with the idea that the hedonicity of the stimulus accounts for activation of analgesia. As Blass and Shah remark, the various studies of human infants, described above, do not directly identify the central mechanisms underlying the modifications in pain responsivity to sucrose taste, but they are consistent with opioid mediation (1995).

Proposed mechanism of chewing induced analgesia

Evidence that chewing analgesia is consistent with serotonergic mediation

The following discussion of serotonin includes a brief outline of serotonergic neuroanatomy, a description of the functions of some of these groups of serotonergic neurons and pathways, and a description of the neuromodulatory role of the serotonergic system on pain. In addition, factors affecting the firing of serotonergic
neurons are outlined to clarify how chewing may be a strategy for activating a descending serotoninergic analgesic system.

**Neuroanatomy**

Within the core of the brainstem lies the reticular formation at whose midline the raphé (i.e. "seam") nuclei cluster (Diamond et al., 1985). It is only within or near the raphé regions of the pons and upper brain stem that cell clusters of serotonin containing neurons can be found (Cooper et al., 1982). Despite the circumscribed location of the cell bodies of most serotoninergic neurons, they project to nearly all areas of the central nervous system (Frazer & Hensler, 1994). It should also be noted that serotoninergic cells are not organized in homogeneous clusters. In fact, the serotonin-designated nuclei contain many nonserotoninergic neurons (Jacobs & Azmitia, 1992). Although the neuroanatomical terminology used to describe the raphé nuclei can be confusing (varying by author and by species considered), the findings summarized below have been confirmed across a variety of species and through numerous histochemical techniques (Willis, 1984).

Nine groups of serotonin-containing neurons, designated B₁ to B₉, were described by Dahlstrom and Fuxe (1964) in the rat through histofluorescent techniques. They correspond to the cytoarchitecturally defined raphé nuclei of the brainstem. The major projections from these serotoninergic groups can be classified roughly as either descending (efferent to the brain) or ascending (afferent to the brain). The six caudal-most groups are the main serotonin cell groups of the inferior serotoninergic clusters that form the main descending serotoninergic projections to the medulla and spinal cord (for details see Willis (1984)). These caudal raphé nuclei include groups B₁ (raphé pallidus), B₂
(raphé obscurus), B3 (raphé magnus), B5, B7 and B9 (Willis, 1984; Rueter et al., 1997; Jacobs & Azmitia, 1992). The more rostral groups (B7 to B9, corresponding to raphé dorsalis, medianus and centralis superior) appear to project to telencephalon and diencephalon. Finally, the intermediate groups may project into both ascending and descending groups (Cooper et al., 1982).

Functions of serotonergic neurons

The putative functions served by the various serotonergic neurons of the raphé nuclei described above can be best summarized in relation to the direction of most of their projections, namely whether they are ascending or descending. Since the present study attempted to recruit a possibly serotonergic subset of neurons thought to play a role in descending analgesia the focus will be on descending projections. Ascending projections will not be discussed beyond mentioning that the main projections supplied by the B7 (raphé dorsalis), B8 (raphé medianus) and B9 groups have been "implicated in physiological processes such as temperature regulation, neuroendocrine function, sleep, arousal and emotion" (Rueter et al., 1997).

Descending serotonergic projections

Of the neurons in groups B1, B3 and B3 at least 73.4% of the serotonergic cells in the rat project spinally and at least 88.6% of spinally projecting neurons contain serotonin (Willis, 1984). Cells from groups B1 to B3 project to all levels of the spinal cord while cell groups B7 and B9 project only to the cervical cord (Willis, 1984). These neurons have been implicated in nociception, autonomic function and the control of motor activity (Rueter et al., 1997).
Serotonergic involvement in pain

Numerous pathways for the descending brainstem to spinal cord serotoninergic projections mentioned above have been described in various species, for example in the monkey (for review see Jacobs & Azmitia, 1992). The termination of one such pathway from the raphé magnus been described in cats. This pathway makes direct contact with neurons in the dorsal horn of the spinal cord that give rise to the spinothalamic tract. The spinothalamic tract is a well described pain transmission and modulation pathway that projects, as its name implies, from the spinal cord to the thalamus. Neurons descending from the raphé magnus, which project to the dorsal, sensory, horn of the spinal cord, are thus thought to modulate the transmission of nociceptive information (Le Bars, 1988; Jacobs & Azmitia, 1992). In fact, some of the most extensively studied networks that modulate nociceptive transmission in the mammalian CNS are those involved in brainstem control of nociception in the spinal cord dorsal horn (Fields et al., 1991). Serotonin, along with noradrenaline and endogenous opioids, is considered to be one of the neurotransmitters most clearly involved in descending control of pain (Stamford, 1995). Serotonin is believed to exert its inhibitory action in the dorsal horn of the spinal cord, but it is not known which type of 5-HT (i.e. serotonin) receptors mediate this antinociceptive effect (Stamford, 1995).

In summary, there is some evidence identifying both ascending and descending (Stamford, 1995) serotonergic involvement in the central regulation of nociception, antinociception and more generally in pain across various mammalian species.
Factors presumably affecting firing of serotonin neurons

One goal of the present study was to evaluate whether chewing could induce analgesia by activating descending, possibly serotonin mediated, analgesia in children. This appeared feasible because of evidence of activation of serotoninergic neurons in non-human subjects. An outline of factors that could affect firing of serotoninergic neurons in animals is given below.

Numerous factors have been examined with respect to their ability to modulate firing of various raphé nuclei neurons in cats. The effects of noxious stimuli and stress, locomotion, feeding and arousal state (sleep/wake) in particular have been studied. Research on animals has shown that repetitive oromotor activity, like that occurring during chewing (or sucking a nipple or pacifier), recruits a subpopulation of caudal raphé serotoninergic neurons (Jacobs & Fornal, 1993). Examples of research using electrophysiological measures to study the firing of serotonin neurons are outlined below followed by microdialysis studies that examined release of serotonin.

Electrophysiological studies

A number of studies suggest that a relationship exists between tonic motor activation, most conspicuously oral-buccal movements (like chewing, licking and sucking) mediated by central pattern generators, and serotoninergic neuronal discharge (Jacobs & Fornal, 1993). Electrophysiological experiments have been done to examine this relationship between behavioural state or motor activation and serotoninergic neuronal discharge. Various authors have examined the effects of behavioural state in mammals and numerous noxious stimuli on firing of raphé nuclei (Veasey et al., 1995; Rueter et al., 1997).
In addition to examining behavioural state and raphé neuronal discharge, researchers have studied the effects of specific behaviours such as locomotor and feeding behaviours on subpopulations of serotoninergic neurons. Certain groups of neurons, within the rostral and caudal raphé nuclei, were found to increase their firing rate when an active animal engaged in locomotor behaviours. Veasey et al., for example, studied locomotor behaviour in cats (1995). By recording in raphé obscurus and raphé pallidus cells, they measured significant elevations in firing from baseline across three increasing treadmill speeds by up to 81.8±22.7% at the highest speed (Veasey et al., 1995). During feeding, when cats engaged in various oral-buccal activities, such as chewing and biting or licking, but not during exposure to inaccessible food, raphé obscurus and pallidus neurons also increased their firing by 66.4±33.7% (Veasey et al., 1995). Feeding behaviours therefore appear able to activate serotoninergic neurons that may be involved in descending analgesia.

As summarized by Rueter (1997) and by Fornal et al. (1997b), electrophysiological studies have underlined the high state-dependence of serotoninergic neuronal activity, the changes in neuronal firing which occur during certain rhythmic motor activities and the relevance of behavioral arousal and motor activity when examining the release of serotonin. Engaging in oromotor activities, such as chewing, may be one potential method for increasing serotoninergic activity. The following section addresses the question: If chewing increases activity in descending serotoninergic projections, does this cause a concomitant increase in the release of serotonin at the spinal level?
Microdialysis

*In vivo* brain microdialysis techniques have produced findings complementary to those generated with electrophysiological methods. Microdialysis has been used to demonstrate that the consequence of increases in neuronal firing indeed appears to be an increase in the release of serotonin (Rueter et al., 1997). The rate of synaptic serotonin release is dependent on the firing rate of serotoninergic soma in the raphé nuclei (Frazer & Hensler, 1994). Thus an increase in firing does entail increased serotonin release.

There is evidence to suggest that changes, most notably increases, in the rate of release of serotonin by raphé neurons are associated with various types of motor activities in the rat. The magnitude of this increase is comparable across brain areas, from cortex to brainstem (Rueter et al., 1997). Reuter et al. reviewed studies of cats in which extracellular serotonin levels were measured using intracerebral microdialysis in relation to motor behaviours (1997). Nine of these studies examined feeding behaviour and found remarkably consistent increases of extracellular serotonin levels ranging from 30% to 150%. The magnitude and direction of change of serotonin levels were consistent across different brain areas, from the prefrontal cortex to the cerebellum, striatum, amygdala, hypothalamus and brainstem. If their findings can be extended to the spinal cord one would expect that activation of serotoninergic neurons (i.e. their increase in firing rate) would entail increased extracellular serotonin release in the spinal cord. Similarly, when rats were engaged in naturalistic behaviours or were exposed to stress, extracellular levels of 5-HT were modified (Rueter et al., 1997). For example, modest increases of extracellular 5-HT levels (between 25-100%) occur during, and often promptly following, behaviours such as feeding (see Rueter et al., 1997). Such research underlines the
relationship between 5-HT levels and specific rhythmic behaviours like feeding (Rueter et al., 1997).

Thus, in addition to the seemingly diffuse and ubiquitous release of 5-HT, which occurs perhaps as a result of general level of arousal rather than specific behavioural changes as outlined above, there also appear to be localized site- or behaviour-specific alterations in 5-HT release (see Rueter et al., 1997 p132).

Summary

In summary, electrophysiological methods used with cats and microdialysis methods used with various species including cats, rats and primates suggest that various stimuli and behaviours, such as locomotion and chewing, can affect firing of serotoninergic neurons and consequently the release of serotonin by these neurons. Anatomical studies of serotoninergic neurons and their involvement in both arousal and behaviours such as oral-buccal movements like chewing (seen in feeding & grooming) and locomotion have led some authors to suggest the existence of two serotoninergic systems (Jacobs & Azmitia, 1992). One system may consist of the typical serotoninergic neurons which, in a behaving animal, fire at a slow steady rate relatively unmodified by numerous behavioural and environmental stimuli. A second system may comprise certain serotoninergic neurons whose activity is significantly increased by particular behaviours, such as rhythmic oral-buccal motor activity, and decreased during orientation to a stimulus (Jacobs & Azmitia, 1992). The latter neurons may be involved in descending serotoninergic projections activated during chewing. It is the close correspondence in time of the neuronal events and the oro-motor activity that is important for the operationalization of the groups in the present study as described in Chapter 2.
Are factors affecting serotonergic firing also affecting pain?

Another relevant question is whether factors that affect firing of serotonergic neurons are the same factors that affect pain. There is indeed evidence in humans and animals connecting gross motor movements with the suppression of sensory transmission (Jacobs & Fornal, 1993). Analgesia induced by 5-HT at the spinal level appears to result concomitantly with repetitive or tonic motor activity (Jacobs & Fornal, 1993). In fact, as outlined above, when repetitive gross motor behaviours mediated by brainstem and spinal cord neurons occur, groups of 5-HT neurons discharge at much higher levels than during a calm awake state. The activation of such neurons associated with chewing or running can be phase-locked to the repetitive motor output. As discussed previously, a number of studies indicate the involvement of central serotonergic neurons in analgesia and in particular those projecting from the nucleus raphé magnus to the dorsal horn of the spinal cord (Jacobs & Fornal, 1995a). It may be through an integrative function of 5-HT brainstem neurons that the inhibition of sensory information, such as pain, occurs.

Sensory information which is “irrelevant” to the generation of motor output, and which could disrupt motor output, could thus be suppressed (Jacobs & Fornal, 1993; Jacobs & Fornal, 1995b). It was therefore hypothesized in this study that chewing would have an analgesic effect in children. This effect may occur through activation of descending serotonergic neurons similar to those triggered by rhythmic oral-buccal movements in cats.

Summary

The two distress and pain modulatory systems discussed above, involving sweet taste and chewing respectively, appear to exist in humans and various animal species.
Their putative mechanisms of action differ, as data from both humans and animals suggests. Sweet taste appears to exert its effect through an endogenous opioidergic system while sucking/chewing may be activating a serotonergic pain modulating system.

Chapter 2: Pain assessment in children and study overview

Types of scales

There are three commonly cited characteristics of pain. the biological, the behavioural and the cognitive, each of which have different indirect measurement strategies (McGrath et al., 1995). Physiological indices used for pain assessment range from heart rate to sweating but none of these indices are commonly used or have been systematically evaluated (McGrath et al., 1995). One reason for this may be their varying degree of invasiveness and the fact that these indicators are not unique to pain.

Discordance between behavioural measures of pain assessment and self-report scales has underlined the need for caution when using behavioural scales to measure and assess pain in children (Beyer et al., 1990; Wong & Baker, 1988).

The established “gold standard” for pain measurement however is self-report (McGrath et al., 1996; McGrath & Unruh, 1989). This is in part due to the fundamentally subjective and private nature of pain as well as the lack of any physiological or behavioural indicator unique to pain. This status of pain as a “latent” variable, a variable which cannot be directly measured, adds to the conceptual difficulty of developing and applying a suitable measure of pain (Champion et al., 1998). This underlines the need for
self-report scales even though they cannot address nociception but only the personal experience of pain (Beyer et al., 1990; Champion et al., 1998).

In the present study, self-report scales were used. In instances of mild to moderate pain such as were seen during the piloting phase of this study, self-report scales can be very effective. In cases of such pain, behavioural rating scales may be of little value since only small responses to the pain which occur may be too subtle to be noticed by observer. Even using self-reports, valid and reliable pain measurement and assessment are difficult endeavours in adults. Using self-reports in children is further complicated by children's greater variability in verbal sophistication and cognitive ability.

A number of review articles were consulted to help select appropriate self-report scales. In a recent paper, Champion (1998) classified and compared 12 categories of self-report scales of pain for adults and children. Scales were compared based on criteria outlined by Price and Harkins (1992). The criteria for good and useful scales were that they have ratio scale properties, be reliable and generalizable, be sensitive to changes in pain intensity, and assess sensory and affective dimensions of pain separately. Scale validity was also evaluated (Champion et al., 1998). These authors concluded that although no uni- or two-dimensional scales meet all criteria, severity of pain is best assessed for research purposes through the combined use of a visual analogue scale like the Coloured Analogue Scale (CAS) (McGrath et al., 1996) and a facial expression scale like the Faces Pain Scale (FPS) (Bieri et al., 1990). These scales have ratio or near ratio qualities. In fact, among facial expression scales, the FPS comes closest to fulfilling the criteria of Price and Gracely (Champion et al., 1998).

Participants in both of the present studies were asked to give self-report ratings of the sensory dimension of the needle pain - its intensity - using the Coloured Analogue
Seale (CAS) (McGrath et al., 1996). They also rated the motivational-affective dimension, or unpleasantness, of the pain with the Faces Pain Scale (FPS) (Bieri et al., 1990). Both scales were selected based on their adequate reliability, validity and scaling properties as outlined below.

The Coloured Analogue Scale (CAS) is an improved version of a more generally used visual analogue scale (VAS) (McGrath et al., 1996). The CAS is a plastic ruler-like device with a tapering triangular shape shading from light red at the bottom to dark red at the top on one side, and a scale from zero at the bottom to 10 (in increments of 0.25) at the top on the other side (see Appendix A). The CAS is minimally intrusive, quick and simple to use and it has equivalent psychometric properties to a 165mm horizontal VAS (McGrath et al., 1996). A cross-modal matching task (rating circle sizes) showed that the CAS also has near ratio-scale properties (McGrath et al., 1996). Its other improvements are that it varies on four qualities, colour, length, width and its vertical orientation, making it more intuitive for children to understand as a scale for rating pain than a simple horizontal VAS. The validity of the CAS was established by comparing it to the properties of the previously validated VAS (McGrath et al., 1996).

The Faces Pain Scale (FPS) consists of a series of seven horizontally-oriented line drawn faces which range from a neutral face to faces demonstrating increasing negative facial affect from left to right (Bieri et al., 1990) (see Appendix B). The scale was developed based on drawings of faces of degrees of pain made by 6 to 10 year old children. Content validity of the FPS is supported by the methods used to generate the faces and construct validity by the published descriptions of facial reactions to pain and formalized coding schedules for these facial reaction in adults (Prkachin, 1992) and infants (Craig & Grunau, 1993; Craig et al., 1993; Craig et al., 1994).
The scales used in this study were selected to be age appropriate for the participants. To increase the likelihood that children would adequately rate their pain with the FPS and CAS, they were given instructions and allowed to practice scale use (see Music Analogies section in Chapter 3).

**Rationale for study and study design**

At present, appropriate existing analgesic methods for minor procedural pain from vaccinations and venepunctures have numerous weaknesses. Topical analgesics such as EMLA® cream, a eutectic mixture of Lidocaine 2.5% and Prilocaine 2.5%, are slow and impractical (must be applied to the skin and left in place covered with an occlusive dressing for at least 1 hr) as well as relatively costly (5g tube costs ~14$). Oral analgesics such as acetaminophen (which is well tolerated, has mild side effects and reaches peak plasma concentrations in 30-60min) are also impractical because they are relatively slow in taking effect (Sunshine & Olson, 1989).

An alternative to pharmacological analgesics could be the use of physiological stimuli whose analgesic action is quick, free of side effects, practical and inexpensive. In infants, maternal contact and breast feeding or administration of a pacifier are easily available “natural” methods of analgesia which have a rapid onset (Gray et al., 2000; Blass & Watt, 1999). In children, a simple non-pharmacological food-like stimulus such as a sweet solution or a sweet gum could also be such a pleasant and practical potential analgesic.

This study consisted of two independent sub-studies referred to as the Blood-draw and Vaccination studies. Subjects in each study were assigned to one of four groups. The four groups and the timing of chewing before or during the procedural pain were
determined based on the characteristics of the anticipated effects of chewing and sweet
taste on pain self-report.

It was desirable that children in all groups chew gum before the painful procedure
to control for any possible expectation effects. If the interventions had no effect beyond
the expectation of an effect from chewing the gum, then one would expect all groups to
have approximately the same ratings, since all chewed gum before the procedure. Based
on effects in newborns (as outlined above), and on the stimulus-bound nature of the
increase in firing of 5-HT neurons from rhythmic oral-buccal movements, the possible
analgesic effects of chewing were anticipated to be “on-off” or “stimulus-bound” in
nature. The analgesic effects of sweet taste, however, were expected to persist for several
minutes after the taste stimulus was no longer present. In term and pre-term infants, the
time of maximal sweet taste antinociception occurs 2 minutes after sucrose termination
(Blass & Shah. 1995; Bucher. 1995). The different time courses of these two stimuli were
thus exploited in the design of the study as follows.

Before the painful procedure, children were randomized to chew (i) unsweetened
gum for 1 min. [Control]. (ii) sweetened gum for 1 min. [Sweet] (iii) unsweetened gum for
2 min. before and during the pain stimulus [Chew] or (iv) sweetened gum for 2 min.
before and during the pain stimulus [Sweet+chew]. Thus, although all groups chew gum,
only Chew and Sweet+chew groups received the Chewing intervention, while Sweet and
Sweet+chew groups received the Sweetness intervention. The Control group, which
chewed unsweetened gum then spat it out and waited 1 minute, therefore received neither
intervention. The potential analgesic effect of chewing would have worn off after 1
minute of not chewing.
Overview of the study

The Blood-draw and Vaccination studies aimed to produce analgesia through the administration of sweet taste, which may occur through a possibly opioid mediated mechanism (discussed above). The studies also attempted to recruit a possible analgesic effect through chewing. It was hypothesized that the analgesic effect of chewing would be mediated by serotoninergic brainstem neurons activated by chewing. Both studies were randomized controlled 2-factorial intervention trials of sweet taste and chewing effects on self-report ratings of pain intensity and affect. The Blood-draw and Vaccination studies differed in their settings (children’s hospital or public school), the participants (patients or students), and the painful stimulus (venepuncture/fingerprick or immunization).

In both settings, pre-adolescent children were given chewing gum. Subjects received either sweet or unsweetened gum and were told to chew either before or before and during a painful stimulus. The control group and the three experimental groups were defined by which gum the children received and for how long they chewed. It was hypothesized that sweet taste would have an analgesic effect that would persist beyond the time during which sweet taste could be detected in the mouth. The analgesic effect of chewing, potentially occurring through serotoninergic action as described above, was expected to be stimulus bound. That is, the analgesic effect of chewing would occur only while a child chewed and would cease when chewing stopped.
Chapter 3: Substudy 1: The Blood-draw study

Objectives of study

The primary objective of this study was to determine whether two physiological stimuli, sweet taste and chewing, would modify and potentially reduce pre-pubescent children’s affect and self-report ratings of pain intensity for “minor” procedural pain. This study predicted that the two stimuli combined would be more effective than either sweet taste or chewing alone. The study has both theoretical and practical relevance.

Theoretical significance of aims

The hypothesized mechanisms modulating sweet taste and chewing analgesia have been suggested based on animal work and studies in some groups of human infants, as discussed above. The experimental groups in this study were created on the basis of the expected time course of the analgesic effects of sweet taste and chewing as determined by studies of infants and by proposed underlying mechanisms for analgesia. If such analgesia were found, this would present convergent evidence supporting the hypothesized opioidergic and serotoninergic mechanisms for analgesia by sweet taste and chewing respectively.

Practical significance of aims

First, a practical objective was to determine whether the analgesic effects of sweet taste and chewing, documented in human and animal infants, are still effective later in development (i.e. in 7 to 11 year old children). Second, if the stimuli were effective, the possibility of their clinical use in this age group would be raised. While this study may allow a broader understanding of how physiological stimuli affect neurotransmitter...
functions and other behaviours. It cannot directly demonstrate the postulated underlying mechanisms of analgesia thought to be recruited by sweet taste and chewing. Generalizability of the findings is strengthened if results are similar across the sub-studies.

Introduction

This study was a randomized controlled 2-factor intervention trial of sweetness and chewing effects on self-report ratings of pain intensity and affect. The setting for the study was the Pediatric Test Center (PTC) (an outpatient sampling service) of the Montreal Children's Hospital. The participants were patients undergoing blood-draw for monitoring or pre-operation reasons.

Methods

Participants

The blood-draw study examined a clinical sample (n=101) of children of ages 7.3 to 12.2 years visiting the PTC for blood collection. Children had blood taken for diagnosis and monitoring (not including oncology). Children were eligible if they (1) spoke English or French fluently (2) had a parent present who gave consent and (3) assented to participate in the study. Both inpatients and outpatients were eligible.

Children were ineligible if they (1) had a fever. (2) were currently in pain. (3) had received analgesics that day (e.g. EMLA or acetaminophen). (4) had allergies to ingredients in the gum or suffered from phenylketonuria (because aspartame used in the gum contains phenylalanine) (Guesry & Secretin, 1991). Children who met criteria for eligibility but were asked, or themselves requested, to lie down at any point in the blood
draw procedure were also excluded from the analysis since lying down was considered a risk for aspiration of the gum. The participant’s weight was measured with a bathroom scale and their height was taken with a wall mounted measuring tape. This information was used to calculate Body Surface Area, as per Selzer et al. (1994). One 60-second egg timer was used to time the chewing.

**Measures**

The Coloured Analogue Scale (CAS) and the Faces Pain Scale (FPS) were used by children to give self-report ratings of pain intensity and ratings of the affective (i.e. unpleasantness) dimension of the needle pain (see Scales section above).

In this study, the FPS faces were coded, from left to right, as 1-7 instead of 0-6 for the sake of simplicity. On the CAS, ratings that fell between the 0.25 gradations were rounded up to the next 0.25 gradation. English and French versions of the CAS, which had word anchors of Most Pain/No Pain and Douleur Très Forte/ Pas de Douleur respectively, were used as appropriate.

A third self-report scale, the Gum Palatability Scale, was created to assess the palatability/hedonicity of the chewing gum. This consisted of a horizontally oriented visual analogue scale with five descriptors spaced evenly over its length: Very good, Good, Fine/So-so, Bad, Very bad (Très bon, Bon, Moyen, Mauvais, Très mauvais). This scale was used to investigate whether palatability of the gum affected children’s pain ratings. This allowed us to assess whether pleasantness of the sweet taste was responsible for analgesia or whether sweet taste alone, regardless of its palatability caused analgesia.
Chewing Gum

The two chewing gums, in the form of wrapped 1g pieces, were manufactured by GumTech International. The sweet gum, sweetened with Aspartame, was approximately as sweet as a 15 to 30% sucrose solution. Psychometric equivalence testing was done whereby 6 solutions of 10, 15, 20, 25, 30, 35% sucrose (g/100ml) were given to an adult subject in alternation with 2 pieces of sweet gum. The subject rinsed their mouth between each 15-second tasting and rated the solutions as “sweeter” or “less sweet” than the gum. The six solutions were cycled through in varied orders three times with one subject and twice with five additional subjects. Solutions of 20% sucrose, and above, were identified 10 out of 13 times as sweeter than the chewing gum suggesting the gum had a subjective sweetness rating falling above a 15% sucrose solution. The unsweetened gum had no sweetener in it. Both gums were unflavoured and had the consistency of commercially available chewing gum. Participants in the study were given two 1g pieces of gum to chew which was comparable to the weight of a typical piece of commercially available chewing gum.

Procedure

We examined all hospital cards of children waiting their turn in the hallway outside the PTC and approached the parent of any child of the appropriate age presenting for blood-draw. The consent form was paraphrased to the parent and child and they were given a copy to peruse. They were assured they would not lose their place in line and that the blood-draw procedure would be completed by the technologist as usual. If consent was given by the parent, and assent by the child, then a card indicating that the patient was going down the hall to participate in the study was placed on the file to notify PTC.
technologists of the patient’s absence. Parent and child were then lead to a room furnished with plants, wall decorations, and padded chairs. In this practice room, the demographic information sheet was completed by the R.A. (See Appendix C). The children were asked to remove their shoes and their weight in kg and height in cm was measured and recorded.

**Music analogies**

To teach participants to distinguish between the intensity of a painful stimulus and the affective qualities of the same stimulus, two analogies from sound perception were used (Goodenough et al., 1999). The two analogies consisted of asking the child to imagine that they heard music playing on the radio. Children were asked to rate the imagined music with the CAS on an intensity dimension (i.e. how loud it was) and with the FPS on an affective dimension (i.e. how it made them feel). The two analogies differed in that one referred to loud music that was pleasant and the other referred to quiet music that was unpleasant. This way the ratings of the imagined music in the analogies would be at opposite ends of the two scales, suggesting a distinction between the intensity of a stimulus and its affective (i.e. pleasant-/unpleasantess) qualities. Unlike Goodenough et al. (1999) however, the connection between the loudness of a song and the intensity of pain as well as that between the unpleasantness of a song and the unpleasantness of pain was not made explicit.

The first music analogy was presented as a training run in which the child was asked to imagine that the research assistant was listening to a song playing on the radio and that this song was playing very loud. The child was then shown the CAS and told that if someone asked the R.A. how loud the music was, he would move the cursor of the CAS...
to within the top half of the scale whose end was labeled Very Loud Music. Next, the child was told to imagine that the same music that was playing was a song that they liked and which made them feel good. They were told that if someone asked the R.A. to point to the face on the scale that showed how he felt when he heard the music, the R.A. would point to the first face because it was a face of someone who felt fine. It was pointed out to them that the other faces showed a person who felt bad.

After the practice round, the participant was told that they would now get a chance to practice using the scales on their own. They were then asked to imagine that they were hearing a new song playing, but this time it was a song that was playing very softly. The child was then asked to rate how loud the music was playing on the CAS with the word anchors “Very Loud Music” at the top and “No Music” at the base of the scale. Subsequently, the child was told that the same song that was playing was a song they did not like and which made them feel bad. The child was then asked to use the FPS to rate how they felt when they heard that song. These two questions were called the Quiet/Unpleasant Music analogy.

Following this the child was given the Loud/Pleasant Music analogy in which they were told that the music was playing very loud but it was music they liked and made them feel good. These analogies were meant to serve as practice in using the CAS and Faces to rate intensity of a stimulus and affective qualities of a stimulus respectively (see Appendix D). These analogies were conceived to teach the child that intensity and affective dimensions of a stimulus are distinct and that a stimulus can have opposite intensity and affective valence. The order of presentation of the music analogies was alternated between participants so that half received the Loud/Pleasant practice analogy followed by the Quiet/Unpleasant and Loud/Pleasant training analogies and others.
received the Quiet/Unpleasant practice analogy followed by Loud/Pleasant and
Quiet/Unpleasant analogies respectively.

The music analogies were only discussed in the training room and not in the PTC.
The training session with the music analogies took under ten minutes. If the child’s
ratings on the scales did not meet pre-determined cutoffs then the child was told the RA
wanted to be sure they understood how to use the scales and the practice analogy was
repeated a second time. The cutoffs were that loud music had to be rated greater than or
equal to five and quiet music had to be rated less than five. Pleasant music had to be rated
as the first face (i.e. the neutral face and the only one not indicating negative affect) and
unpleasant music could be any face but the first. If after the second repetition the child
did not give correct ratings the experiment was done to completion but the child was
considered as having had difficulty with the scale instructions. as per Goodenough et al. (1997),
and their data was excluded from analysis. Children who had difficulty were
allowed to continue with the experiment in order not to stigmatize them by telling them
they were being dropped from the study.

Blood-draw

Before the blood-draw, participants were randomized in blocks of eight to one of
four groups: Control, Sweet, Chew or Sweet+chew. Control and Chew groups chewed
unsweetened gum while Sweet and Sweet+chew groups chewed sweetened gum. The
R.A. and technologist were blind to the sweet dimension of the experimental condition of
the participant. That is, the R.A. only knew whether the participant had to spit out the
gum after 1 min. or whether they had to chew throughout the procedure but did not know
whether the gum was sweet or not and therefore could not extrapolate which experimental
group the participant was in. The blinding was done by having another RA pre-code the chewing gum with a number and a letter, either S or K, indicating that the gum should be “spat” out after 1 min. or “kept” during the procedure respectively. The participants were also asked not to divulge whether the gum they were chewing was sweet so the R.A. was not inadvertently unblinded.

Upon return from the practice room the parent and child were again seated in the hallway and the technologist was notified of their return. The technologist was told how long the child would be chewing gum and how long they were requested to wait before performing the blood-draw. Technologists were also encouraged to remind the children to chew the gum. When called by the technologist, the parent and child entered the clinic. The child was seated and then asked: “I’d like you to point to the face that shows me how you feel right now”. This FPS score was recorded as the baseline affect rating and the child was then given their gum to chew. Children in Control and Sweet groups spat out their gum after 1 min. and waited another minute while looking at a 60-second hourglass. Children in Chew and Sweet+chew groups chewed throughout the procedure. Children in Control and Sweet groups spat out their gum after 1 min. and then waited 1 min. before the blood-draw. After 2 min. had elapsed, the venepuncture or fingerprick was performed by one of eighteen available technologists using a standard 23-gauge butterfly needle and Vacutainer tubes or a Microtainer safety-flow spring-loaded lancet for the blood-draw. As soon as possible after the needle left the child’s arm or their finger was released, and as the site was being covered with an adhesive bandage, the participant’s self-report ratings of pain intensity and affect were obtained. The R.A. leaned over and asked the child to spit out their gum if they were in the Chew or Sweet+chew groups. The R.A. then held up the CAS and said. “I’d like you to show me how much pain you just had during the
needle”. Then the child was shown the Faces scale and asked: “and now I’d like you to point to the face that shows me how you just felt during the needle” (see Appendix E for scripts). The child was then asked to rate the chewing gum on the Gum Palatability Scale. After this, both child and parent were thanked for having participated in the study.

Statistics

Power calculations were performed with the power analysis computer program PASS 6.0 by NCSS. To have power of at least 0.80 for the testing of the primary hypotheses, with an estimated medium effect size of .25, defined by Cohen as an effect which could be visible to the naked eye of a careful observer (1992), group size of 25 for each of the four groups in this study was chosen (alpha set at 0.05). In the blood-draw study, where group size was 23 or more, power was at least 0.80.

Statistical analysis was performed with JMP 3.2.5 software. The criterion for statistical significance for analyses was $P < 0.05$. When multiple pairwise comparisons were made $P < 0.01$ was considered significant to control for inflated risk of Type-I error.

To verify whether the randomization of participants to groups resulted in significant differences with regard to a number of demographic variables, we tested for differences between the four experimental groups on the following variables: age, sex, Body Surface Area (BSA), mother-tongue, preferred language, reasons for blood test, previous painful procedures, number of days of hospitalization, technologist performing blood-draw, research assistant attending, behaviour during blood-draw, type of blood-draw procedure performed and baseline affect self-report rating (on FPS). Either t-tests, for continuous variables, or Chi-square tests, for categorical variables, were performed.
Variables that differed significantly across groups were controlled for in later analyses (i.e. used as covariates in ANCOVA models).

Initial analysis consisted of an omnibus 3-factor (2 (Sex) X 2 (Sweet) X 2 (Chew) with Age as a covariate) ANCOVA procedure to test for main effects or interaction effects of sweet taste and chewing in relation to sex on the two self-report outcome variables: Coloured Analogue Scale (CAS) pain intensity rating (ranging from 0 to 10) and Faces Pain Scale (FPS) pain unpleasantness rating (ranging from 1 to 7).

Subsequent analysis consisted of 2-factor (2 (Sweet) X 2 (Chew) with Age as a covariate) ANCOVA procedures done separately by sex. This analysis was repeated across sex. Post-hoc pairwise and multiple comparisons were then done to compare the pain ratings of the individual groups when significant interactions were found.

In addition, the correlation of baseline ratings of affect (given by self-report on the FPS) with the two self-report outcome variables (i.e. the CAS pain intensity rating and FPS pain unpleasantness rating) was examined. This analysis was done separately by sex.

**Ethical considerations**

The protocol for both sub-studies was approved by the Montreal Children’s Hospital Research Ethics Board and by the principals of the schools involved. Children receiving blood-draws or vaccinations who requested to lie down, or were told to do so by a nurse or medical technologist, were asked to spit out their gum to avoid accidental aspiration. Nurses, technologists and research assistants were reminded of this. Children who requested to spit out the gum were also welcomed to do so. The data from such participants was excluded from the analysis.
Parents were given letters and consent forms outlining the study and were encouraged to ask the research assistant any questions they had (see Appendices F and G). Children were asked for assent to participate in the study and their questions were answered by the research assistant during the recruiting. The consent form listed the telephone number and name of the principal investigator responsible for the study.

Results

Demographic variables

Table 1 provides details of the characteristics, and Table 2 of the needle and hospital experience, of children who successfully completed the blood-draw study.

Table 1: Characteristics of Sample (Blood-draw study)

<table>
<thead>
<tr>
<th>Characteristics by group</th>
<th>Control n=28</th>
<th>Sweet n=25</th>
<th>Chew n=23</th>
<th>Sweet+chew n=23</th>
<th>Total N=99(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [range: 7.3-12.2] *</td>
<td>Mean± 10.5± 9.7± 10.2± 9.6± 10.0±</td>
<td>1.2 1.2 1.1 1.3 1.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>Male 18 10 11 10 49 (49.5%)</td>
<td>10 15 12 13 50 (50.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 15 12 13 50 (50.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean± 144± 10 140± 141± 138± 141±</td>
<td>10 10 8 10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean± 40.1± 38.3± 36.9± 35.3± 37.8±</td>
<td>11.4 14.1 10.9 8.2 11.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Surface Area [BSA] (m²)</td>
<td>1.3± 1.2± 1.2± 1.2± 1.2±</td>
<td>0.21 0.27 0.21 0.17 0.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother tongue of child</td>
<td>English 10 9 8 13 40</td>
<td>French 13 10 9 6 38</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5 6 6 4 21</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preferred language</td>
<td>English 13 11 9 14 47</td>
<td>French 15 14 14 9 52</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are number per group or mean ± standard deviation. *Groups differed significantly on Age, P< .05

46
### Table 2: Needle and Hospital Experience of Sample (Blood-draw study)

<table>
<thead>
<tr>
<th>Characteristics of participants by group</th>
<th>Control n=28</th>
<th>Sweet n=25</th>
<th>Chew n=23</th>
<th>Sweet+chew n=23</th>
<th>Total N=99(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reason for blood test</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before operation</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Monitoring of drug level</td>
<td>7</td>
<td>3</td>
<td>8</td>
<td>5</td>
<td>23 (23.2)</td>
</tr>
<tr>
<td>Check-up for chronic illness</td>
<td>5</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>15 (15.2)</td>
</tr>
<tr>
<td>Investigation for unknown illness</td>
<td>13</td>
<td>16</td>
<td>11</td>
<td>13</td>
<td>53 (53.5)</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>6 (6.0)</td>
</tr>
<tr>
<td>Previous painful sampling</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venepuncture/fingerprick</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either in past week</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>6 (6.1)</td>
</tr>
<tr>
<td>Number in Past year (includes past wk.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6</td>
<td>13</td>
<td>7</td>
<td>13</td>
<td>39 (39.4)</td>
</tr>
<tr>
<td>1-5</td>
<td>18</td>
<td>9</td>
<td>12</td>
<td>7</td>
<td>46 (46.5)</td>
</tr>
<tr>
<td>6 and more</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>14 (14.1)</td>
</tr>
<tr>
<td>Other needle procedure (past year)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunization</td>
<td>4</td>
<td>8</td>
<td>9</td>
<td>4</td>
<td>25 (25.3)</td>
</tr>
<tr>
<td>Other injection</td>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>8 (8.1)</td>
</tr>
<tr>
<td>Intravenous</td>
<td>4</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>11 (11.1)</td>
</tr>
<tr>
<td>Lumbar puncture / bone marrow aspiration</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>None</td>
<td>19</td>
<td>15</td>
<td>13</td>
<td>17</td>
<td>64 (64.6)</td>
</tr>
<tr>
<td>Days in hospital (in past 2 years)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>16</td>
<td>18</td>
<td>17</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2-7</td>
<td>3</td>
<td>2</td>
<td>5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>13-120</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Behaviour during venepuncture/fingerprick</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous looking</td>
<td>7</td>
<td>7</td>
<td>12</td>
<td>13</td>
<td>46 (46.5)</td>
</tr>
<tr>
<td>Spontaneous non-looking</td>
<td>16</td>
<td>15</td>
<td>11</td>
<td>9</td>
<td>51 (51.5)</td>
</tr>
<tr>
<td>Instructed on looking</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>Blood-draw procedure performed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venepuncture (arm)</td>
<td>22</td>
<td>15</td>
<td>15</td>
<td>12</td>
<td>64 (64.6)</td>
</tr>
<tr>
<td>Finger-prick</td>
<td>6</td>
<td>10</td>
<td>8</td>
<td>11</td>
<td>35 (35.4)</td>
</tr>
<tr>
<td>Baseline affect rating</td>
<td>Mean± 1.96± 2.08± 2.0± 2.26± 2.07±</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>1.20± 1.41± 1.09± 1.48± 1.29±</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(FPS) [range: 1-7]</td>
<td></td>
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</tbody>
</table>
Out of 134 children who gave assent and whose parents consented to the study, 102 completed the experiment and only three failed the music analogy leaving 99 usable data points (97%). The most common reason for not completing the experiment was requesting or being told to lie down since this required children to spit out their gum (n=24). In addition, one child spat the gum too early, another refused to chew, and 6 did not complete the study properly. Passing the music analogy consisted of answering both questions on the two music-analogies correctly in one or two tries. One child failed the music analogy when they needed the music analogy repeated three times. The other two children who failed the music analogy did so because they did not select face number one of the FPS as the face showing someone who felt fine.

Age was the only demographic variable on which groups differed significantly (F=3.34 (df 3.95), p=0.02). No differences were found between groups on all other demographic variables listed in Table 1. The Control group was significantly older than the Sweet group and the Sweet+chew group (mean ± S.D.: Control: 10.5±1.2; Sweet: 9.7±0.24; Sweet+chew: 9.6±1.3; Pairwise comparison using Student's t = 1.98, P < 0.05). There were no significant differences between the groups on any characteristics relating to their needle and hospital experience (Table 2), therefore these variables were not included in subsequent analyses.

Behaviour during blood-draw was recorded to examine whether it affected children's pain ratings, perhaps reflecting a type of coping behaviour. There were no significant differences on CAS ratings among children who spontaneously looked at the site of sampling, those who did not look spontaneously, and those who were instructed either to look or not look (mean ± SD: looker 3.77±3.1, non-looker 3.66±1.94, instructed
4.13±4.42; F=0.05 (df 2.96). There were also no significant differences on FPS ratings (mean ± SD: looker 2.59±1.61, non-looker 2.2±1.2, instructed 2.5±2.12; F=0.90 (df 2.95), p=0.41).

There were no significant differences on the pain ratings on the CAS between children receiving venepuncture or finger-prick blood sampling (mean ± SD: arm venepuncture 3.46±2.71, finger-prick 3.86±2.48; t=-0.741, p=0.46). There were also no differences on pain affect ratings on the FPS (mean ± SD: arm venepuncture 2.26±1.48, finger-prick 2.46±1.39; t=-0.677, p=0.5). Because no differences were observed between groups by the type of painful procedure received (i.e. venepuncture or fingerprick), subsequent analyses combined the data of children who had received venepunctures with children who had received finger-prick blood sampling.

There was no difference between the groups in terms of which of 15 technologists performed the blood-draw or which of two research-assistants attended (data not shown), although the power to detect a difference between the technologists was obviously low. Age and pain intensity self-report ratings (CAS) were significantly correlated, as were age and pain affect self-report ratings (FPS) (CAS: r (99) =-0.24, p=0.02; FPS: r (98) =-0.22, p=0.03). However unlike Goodenough et al. (1997b), Body Surface Area (BSA) and pain intensity self-report ratings (CAS) were not significantly correlated, nor were BSA and pain affect self-report ratings (FPS) (CAS: r (99) =-0.16, p=0.11; FPS: r (98) =-0.08, p=0.45). Age and BSA were significantly correlated (r (99) =0.5, p<0.01). In addition, CAS and FPS ratings were significantly correlated (r (98) = 0.53, p<0.01) which was similar to correlations between pain and distress reported by Fradet et al. (1990).
Sweet taste and chewing

Effects of Sweet taste and Chewing by Sex on pain ratings

Three-factor ANCOVA procedure (2 (Sex) X 2 (Sweet) X 2 (Chew) with Age as a covariate) was performed.

There were no significant main effects on the CAS pain intensity rating for either sex (F=1.62 df (1.89), p=0.21), sweet taste (F=0.58 df (1.89), p=0.45) or chewing (F=3.15 df (1.89), p=0.08). None of the two-factor interactions between sex and sweet taste (F=0.69 df (1.89), p=0.41), sex and chewing (F=0.89 (df 1.89), p=0.35), or sweet taste and chewing (F=0.01 df (1.89), p=0.94) were significant. The three-factor interaction between sex and sweet taste and chewing was also not significant (F=1.13 (df 1.89), p=0.29).

With respect to the FPS pain affect rating, the analysis did not reveal main effects for sex (F=1.62 (df 1.89), p=0.21), sweet taste (F=0.58 (df 1.89), p=0.45) or chewing (F=3.15 (df 1.89), p=0.08). The two-factor interactions between sex and sweet taste (F=2.17 (df 1.89), p=0.14), sex and chewing (F=0.76 (df 1.89), p=0.39), or sweet taste and chewing (F=1.06 (df 1.89), p=0.31) were not significant. There was however a significant three-factor interaction between sex and sweet taste and chewing (F=8.09 (df 1.89), p=0.006). Because of this interaction, subsequent analyses were done separately by sex as outlined below.

Analyses separated by sex

Males
Because the three-factor ANCOVA on the CAS was not significant, no two-factor ANCOVA for male data only was performed. However, the data are plotted for the purpose of comparison (see Fig. 1).

Two-factor ANCOVA procedure revealed that with regard to the FPS for males there were no main effects of either sweet taste \((F=2.33 \text{ (df 1.44), } p=0.13)\) or chewing \((F=0.16 \text{ (df 1.44), } p=0.69)\). There was however a significant interaction between sweet taste and chewing on pain affect ratings on the FPS \((F=8.04 \text{ (df 1.44) } p=0.007)\) (see Fig. 2).

Of particular interest was the pattern of responses in males. For both CAS and FPS ratings chewing *reduced* pain ratings and sweet taste *increased* pain ratings (see Fig. 1 and 2).

Subsequently, post-hoc comparisons revealed that, in males only, the chew group had significantly lower scores on the FPS than the combined group which was not significantly different from controls but worse than the other groups \((t=-2.99, p=.005; t=1.44 \text{ (p =0.16); } t=2.65, p=.01)\).

Females

Because the three-factor ANCOVA on the CAS was not significant, no two-factor ANCOVA for female data only was performed. However, the data are plotted for the purpose of comparison (see Fig. 3).

Two-factor ANCOVA procedure \(2 \text{ (Sweet) } \times 2 \text{ (Chew) with Age as a covariate}\) on the FPS in females revealed a main effect of chewing, with the chew group reporting higher pain affect ratings \((F=3.98 \text{ (df1.46), } p=0.05)\). There was no main effect of sweet taste \((F=0.05 \text{ df1.46), } p=0.83)\). There was no significant interaction between sweet taste and chewing in females \((F=1.77 \text{ df1.46), } p=0.19)\) (see Fig. 4).
In females, a distinct pattern of responses, opposite to that described in males above, was observed. Namely, chewing increased pain ratings and sweet taste reduced pain ratings (but only in one of two cases) (see Fig. 3 and 4).

Effects of Sweet taste and Chewing across Sex on pain ratings

During blood-draw, on the CAS there was no statistically significant main effect of sweet taste (F=0.01 (df 1.96), p=0.92). There was no significant main effect of chewing (F=0.05 (df 1.96), p=0.83). There was also no significant interaction between sweet taste and chewing (F=0.05 (df 1.96), p=0.83) (see Fig. 5).

On the FPS there was no significant main effect for sweet taste (F=0.15 (df 1.94), p=0.7). There was no significant main effect for chewing (F=2.15 (df 1.94), p=0.15). There was also no significant interaction between sweet taste and chewing (F=1.19 (df 1.94), p=0.28) (see Fig. 6).

Thus, when the data was examined without considering sex, no evidence was found to support the hypothesis that sweet taste or chewing or the combination significantly reduce pain ratings on either self-report scale.

Correlations of Baseline FPS with post-needle pain ratings

In females and males, baseline affect ratings (FPS) were significantly correlated with pain affect ratings (FPS) (i.e. after blood-draw). Baseline affect ratings however were not significantly correlated with pain intensity ratings (CAS) after blood-draw (Table 3).
Table 3: Correlations between Baseline affect ratings (FPS) and the Dependent Variables

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinic CAS</td>
<td>.22</td>
<td>.08</td>
</tr>
<tr>
<td>FPS</td>
<td>.30*</td>
<td>.38**</td>
</tr>
</tbody>
</table>

Note: Values are Pearson product-moment correlations.
*P<.05. **P<.01.

Gum palatability ratings

Out of 48 children who chewed sweet gum, 10 rated the gum as "Very good", 12 "Good", 18 "Fine/So-so", 4 "Bad", and 3 "Very Bad". Data was missing for one child.

Out of 51 children who chewed unsweetened gum, 6 rated the gum as "Very good", 8 "Good", 17 "Fine/So-so", 8 "Bad", and 10 "Very Bad". Data was missing for two children.

When only data from the subset of children who rated the chewing gum as either "good" or "very good" were used, significant differences were observed between groups. Specifically two-factor ANOVA revealed that on the CAS there were no significant main effects of either sweet taste (F=0.01 (df3,32), p=0.91) or chewing (F=3.00 (df3,32), p=0.09). However, there was a significant interaction of sweet taste and chewing (F=7.43 (df3, 32), p=0.01). Post-hoc pair-wise comparisons revealed that the Chew group had lower pain ratings than Controls and lower ratings than the Sweet+chew group (t=-2.8, p=0.009; t=2.22, p=0.03).

Two-factor ANOVA procedure revealed that on the FPS there were no significant main effects of either sweet taste (F=0.83 (df3,32), p=0.37) or chewing (F=0.23 (df3,32).
p=0.63). There was no significant interaction of sweet taste and chewing (F=3.2 (df3. 32), p=0.08).

**Summary**

There was a significant omnibus three-factor ANCOVA (2 (Sex) X 2 (Sweet) X 2 (Chew) with Age as a covariate) for FPS but not for CAS. Consequently, we split subsequent ANCOVAs by sex. In these separate analyses (Fig. 1-4) sweet gum use tended to *increase* pain ratings when chewed by males, but *decrease* (or not change) pain ratings when chewed by females. Unsweetened gum had the opposite effect when chewed in that it *reduced* pain ratings in males and *increased* pain ratings in females. This trend was only *statistically* confirmed for FPS ratings in males where the Sweet+chew group had significantly higher pain affect ratings than the Chew group. The Sweet+chew group was not significantly different from Controls but worse than the other groups. The opposite trend seen in females was *statistically* confirmed for FPS ratings with a main effect of chewing where the Chew group reported higher pain affect ratings.

**Chapter 4: Substudy 2: The Vaccination study**

**Objective**

The objectives for the vaccination sub-study were identical to those of the blood-draw sub-study, as outlined above.

**Introduction**

This study was a randomized controlled 2-factor intervention trial of sweet taste and chewing effects on self-report ratings of pain intensity and affect. The setting for the
The study was two public primary schools in Châteauguay, Québec. The participants were students having their first Hepatitis B intramuscular immunization administered to them by nurses from the CLSC Samuel-de-Champlain of the Montérégie Health Board.

**Methods**

**Participants**

The vaccination study recruited 115 students in grade 4 receiving their 1st Hepatitis B immunization at École Laberge and École St-Jude in Châteauguay. The sample consisted of 64 males and 51 females (age mean±SD: males 9.62±0.41, females 9.66±0.47 years). Children were not acutely ill, not receiving medications, and had signed informed consent from their parents (solicited separately from but at the same time as consent for immunization). Culturally the children are almost exclusively francophone Québécois. Parents were not present during vaccination.

**Measures**

The same self-report scales as in the blood-draw study were used. Three 60-second egg timers were used to time the chewing.

**Chewing Gum**

The same two types of chewing gum were used as in the blood-draw study.

**Procedure**

Consent forms were distributed to all children in grade four in each of three classes at both schools. All children whose parents signed the consent form and who assented to participate in the study were given a 15 minute practice session on the
Thursday preceding the October 15th 1999 vaccination at École Laberge and on the Friday preceding the October 25th 1999 vaccination at École St-Jude. Two R.A.s presented themselves to the students and handed out three sheets of paper. Each child was given one white, one pink and one green paper with a black and white laser copy of a CAS with the anchors Very Loud Music and No Music on one side and a copy of the Faces scale on the other.

**Practice sessions**

The in-class practice sessions consisted of presenting three music analogies to the students and asking them to rate the music intensity and unpleasantness on the CAS and Faces respectively. The children were read the script in Appendix H. They were distributed all three photocopies and asked to write their names on the sheets. They were also asked not to look at their neighbours’ scores and reassured that this was not a test. The first music analogy was presented as a training run in which the children were asked to imagine that they heard very loud music playing. Then they were shown a 25.7 by 39.6-cm photocopy of the CAS and told that if we asked one of the R.A.s how loud the music is she would draw a line at the top of the scale on the end which says Very Loud Music. The R.A. then drew the line on the photocopy and asked the children to follow suit on their white copy. They were then shown the back of the 25.7 by 39.6-cm photocopy and told to turn their copy over. The students were then told to imagine that the same music that was playing was a song that they liked and which made them feel good. They were told that if we asked one of the R.A.s to circle the face on the scale that showed how they felt when they heard the music they would circle the first face because it was a face of someone who felt good. It was pointed out to them that the other faces
showed people who felt bad. Then they were told they would get a chance to practice on their own.

The next music analogy whose scores they marked on the pink photocopied paper referred to music which played quietly but which they did not like and which made them feel bad. The last analogy was the same as the first but they were told to record their scores on the green sheet of paper. At the end of the procedures, questions regarding participation in the study were entertained and the children and teachers were thanked for their participation.

Vaccination sessions

On October 15th seven research assistants set-up three data collection stations in the library where the vaccinations were to take place at École Laberge. Vaccination lasted from 9a.m. to 11a.m.. The teachers re-distributed the signed consent forms to the students so that, when the students presented themselves to the intake table, they handed their vaccination consent to a nurse and the signed study consent to one research assistant. The R.A. then gave them a pre-numbered sticker and wrote their name on it. Each participant therefore had a unique participant number, recorded next to their name on a class list, that was pre-assigned to one of four conditions: Control, Sweet, Chew or Sweet+chew. Children without completed consent forms were given a sticker with only their name on it and were directed straight to the next available spot at one of the three nurses’ vaccination stations. Participants in the study however sat and waited for their turn at one of three baseline stations.

At the baseline station, the participant was greeted and one last music analogy, involving either loud and pleasant music or quiet and unpleasant music, was presented to
them as a final practice of the CAS and Faces scales (see script in Appendix 1). They were then asked to rate how they felt at that moment using the Faces scale. This was recorded as their baseline level of affect. Depending on their participant number they were then given either two pieces of sweet or unsweetened gum to chew and were asked to watch a 60-second egg timer. Once the time had elapsed, children in the Sweet and Control groups were asked to spit their gum into the garbage. Children then proceeded to one of three vaccination stations staffed by nurses. Vaccination consisted of intramuscular injection of Recombivax Hepatitis B serum into the deltoid of the non-dominant arm of the child. Children received 0.25 cc of serum delivered through a 26 gauge needle and a 5/8th inch syringe. Children over 11 years of age received 0.5 cc from a 1-inch syringe. The nurses carried out the vaccinations as they had been trained to, but were also asked to encourage those children with gum to chew. Immediately after the needle left the child’s arm an R.A. approached the child, asked them to spit out their gum, and said: “I’d like you to show me how much pain you just had during the needle”. The child was then shown the Faces scale and asked; “and now I’d like you to point to the face that shows how you just felt during the needle” (see Appendix 1).

Statistics

Sample size was set at 120 and alpha set at 0.05 to allow power of .80 which was calculated in advance using the PASS program with an estimated medium effect size of .25.

As in the blood-draw study, to have power of at least 0.80, expecting an effect size of 0.30, a group size of 25 for each of the four groups in this study was chosen (alpha set
at 0.05). In the vaccination study, there were at least 27 participants per group. With alpha set at 0.05 and effect size of 0.30, power was calculated to be at least 0.86.

An omnibus 3-factor (2 (Sex) X 2 (Sweet) X 2 (Chew)) ANOVA procedure was performed to test for main effects or interaction effects of sweet taste and chewing in relation to sex on the two self-report outcome variables: Coloured Analogue Scale (CAS) pain intensity ratings and Faces Pain Scale (FPS) pain unpleasantness rating.

Subsequent analysis consisted of 2-factor (2 (Sweet) X 2 (Chew)) ANOVA procedures done separately by sex. This analysis was repeated across sex. Post-hoc pairwise and multiple comparisons were then done to compare the pain ratings of the individual groups when significant interactions were found.

In addition, the correlation of baseline ratings of affect (given by self-report on the FPS) with the two self-report outcome variables (i.e. the CAS and FPS pain ratings) were examined. This analysis was done separately by sex.

Results

We tested for differences between the four experimental groups on age and sex. Either t-tests for continuous variables, or Chi-square tests for categorical variables, were performed. Neither variable was significantly different across groups so age and sex were not used as covariates.

Demographic variables

Table 4 provides details of the characteristics of children who successfully completed the Vaccination study.

Table 4: Characteristics of sample (Vaccination study)
### Characteristics by group

<table>
<thead>
<tr>
<th>Characteristics by group</th>
<th>Control n=30</th>
<th>Sweet n=28</th>
<th>Chew n=30</th>
<th>Sweet+chew n=27</th>
<th>Total N=115</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Mean±</td>
<td>9.64±</td>
<td>9.61±</td>
<td>9.63±</td>
<td>9.67±</td>
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<tr>
<td>[range: 9-11]</td>
<td>SD</td>
<td>0.44</td>
<td>0.43</td>
<td>0.49</td>
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<td>16</td>
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<td></td>
<td>Female</td>
<td>15</td>
<td>12</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Baseline affect rating (FPS) [range: 1-7]</td>
<td>Mean±</td>
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<td>2.21±</td>
<td>2.47±</td>
<td>1.93±</td>
</tr>
<tr>
<td></td>
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<td>1.43</td>
<td>1.5</td>
<td>1.8</td>
<td>1</td>
</tr>
</tbody>
</table>

In the vaccination sub-study, of 135 children who gave assent and whose parents consented to the study, 121 completed the experiment. Of those, only 6 failed the music analogy, leaving 115 (85%) for inclusion in further analyses.

Fewer types of data were gathered in the vaccination study, compared to the blood-draw study, because of the nature of the setting (i.e. vaccination of entire classrooms at a time vs. one-on-one blood-draws in hospital). CAS and FPS pain ratings were significantly correlated ($r (115) = 0.64, p<0.01$).
Effects of Sweet taste and Chewing considering Sex on pain ratings

A three-factor ANOVA procedure (2 (Sex) by 2 (Sweet) by 2 (Chew)) was performed.

There were no significant main effects on the CAS pain intensity rating for either sex (F=0.30 df (1.108), p=0.58), sweet taste (F=1.06 df (1.108), p=0.31) or chewing (F=0.34 df (1.108), p=0.56). None of the two-factor interactions between sex and sweet taste (F=1.17 (df 1.108), p=0.28), sex and chewing (F=1.14 (df 1.108), p=0.29), or sweet taste and chewing (F=0.47 (df 1.108), p=0.5) were significant. The three-factor interaction between sex and sweet taste and chewing however was significant (F=4.63 (df 1.108), p=0.03).

With respect to the FPS pain affect rating, the analysis did not reveal main effects for sex (F=2.0 (df 1.108), p=0.16), sweet taste (F=0.47 (df 1.108), p=0.5) or chewing (F=0.2 (df 1.108), p=0.66). The two-factor interactions between sex and sweet taste (F=0.75 (df 1.108), p=0.39), and sex and chewing were not significant (F=1.05 (df 1.108), p=0.31). There was however a significant three-factor interaction between sex and sweet taste and chewing (F=4.66 (df 1.108), p=0.03). Because of these interactions, subsequent analyses were done separately by sex.
Analyses separated by sex

Males

Two-factor ANOVA procedure revealed that on the CAS for males there were no significant main effects of either sweet taste ($F=2.46$ (df1.61), $p=0.12$) or chewing ($F=1.5$ (df1.61), $p=0.23$). There was however a significant interaction of sweet taste and chewing ($F=4.44$ (df1.61), $p=0.04$) (see Fig. 7).

Likewise on the FPS for males there were no main effects of either sweet taste ($F=0.02$ (df1.61), $p=0.88$) or chewing ($F=0.23$ (df1.61), $p=0.63$) but there was a significant interaction of sweet taste and chewing ($F=4.49$ (df1.61), $p=0.04$) (see Fig. 8).

As in the previous sub-study, a similar response pattern was seen in males. For both CAS and FPS ratings sweet taste increased pain ratings and chewing reduced pain ratings (see Fig. 7 and 8).

Post-hoc pairwise comparisons revealed that in males, the Chew group had significantly lower pain intensity ratings on the CAS than the Sweet+chew group which was no different from Controls ($t=-2.64$, $p=0.01$; $t=0.24$, $p=0.81$).

Females

Two-factor ANOVA procedure revealed that on the CAS for females there were no significant main effects of either sweet taste ($F=0.001$ (df1.48), $p=0.97$) or chewing ($F=0.11$ (df1.48), $p=0.74$). There was no interaction of sweet taste and chewing ($F=1.00$ (df1.48), $p=0.32$) (see Fig. 9).

On the FPS for females there were no main effects of either sweet taste ($F=0.87$ (df1.48), $p=0.36$) or chewing ($F=0.78$ (df1.48), $p=0.38$) and no significant interaction of sweet taste and chewing ($F=1.14$ (df1.48), $p=0.29$) (see Fig. 10).
In females, a distinct pattern of responses, opposite to that described in males above, was observed as in the previous sub-study. Namely, sweet taste *reduced* pain ratings and chewing *increased* pain ratings (see Fig. 9 and 10).

Post-hoc tests did not reveal any significant differences between groups on the FPS in males or in females.

**Effects of Sweet taste and Chewing across Sex on pain ratings**

During vaccination, on the CAS, there was no statistically significant main effect of sweet taste (\(F=1.54\) (df 1.112), \(p=0.22\)). There was no significant main effect of chewing (\(F=0.42\) (df 1.112), \(p=0.52\)). There was also no significant interaction between sweet taste and chewing (\(F=0.87\) (df 1.112), \(p=0.35\)) (see Fig. 11).

On the FPS there was no significant main effect for sweet taste (\(F=0.28\) (df 1.112), \(p=0.6\)). There was no significant main effect for chewing (\(F=0.12\) (df 1.112), \(p=0.73\)). There was also no significant interaction between sweet taste and chewing (\(F=0.41\) (df 1.112), \(p=0.52\)) (see Fig. 12).

Thus, when the data was examined without considering sex, no evidence was found to support the hypothesis that sweet taste or chewing or the combination significantly reduce pain ratings on either self-report scale.

**Correlations of Baseline FPS with post-needle pain ratings**

In females only, baseline affect ratings (FPS) were significantly correlated with affect ratings and with pain intensity ratings (CAS) after vaccination (Table 5).
Table 5: Correlations between Baseline affect ratings (FPS) and the Dependent Variables

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>School CAS</td>
<td>.05</td>
<td>.37**</td>
</tr>
<tr>
<td>FPS</td>
<td>.05</td>
<td>.65***</td>
</tr>
</tbody>
</table>

Note: Values are Pearson product-moment correlations. **P<.01. ***P<.001.

Summary

Both omnibus three-factor ANOVAs (2 (Sex) X 2 (Sweet) X 2 (Chew)) were significant for CAS and FPS. We therefore separated subsequent ANOVAs by sex. As in the previous sub-study, in these separate analyses (Fig. 7-10) sweet gum use tended to increase pain ratings when chewed by males, but decrease pain ratings when chewed by females. Unsweetened gum had the opposite effect when chewed in that it reduced pain ratings in males and increased pain ratings in females. This trend was only statistically confirmed for CAS and FPS ratings in males. The male and female pattern appears to account for the three-factor (Sex x Sweet x Chew) interaction seen. Because the effects of sweet taste and chewing were small, no statistically significant effects were found for sweet taste, chewing or their interaction when analyzed across sex.

Chapter 5: General Discussion

Main hypotheses

The three-factor Sex by Sweet taste by Chew ANCOVAs in the blood-draw study and ANOVAs in the vaccination study revealed sex related differences in pain self-report by condition. A consistent pattern of responses, which differed in boys and girls, was repeated across both sub-studies on both the CAS and FPS. Namely, in boys, sweet gum
tended to increase pain ratings when chewed, while unsweetened gum decreased pain ratings when chewed. In girls, these ratings had opposite trends in that sweet gum tended to decrease (or not change) pain ratings when chewed, while unsweetened gum increased pain ratings when chewed (see Figs. 1.2.7.8 and 3.4.9.10 respectively). Furthermore, this pattern was statistically significant in three out of four of the three-factor Sex by Sweet by Chew interactions in the blood-draw and vaccination sub-studies. In the blood-draw sub-study on the FPS, but not the CAS, the three-factor ANCOVA was statistically significant. In the vaccination sub-study both the FPS and CAS the three-factor ANOVAs were statistically significant.

Not surprisingly, when pain ratings were analyzed across sex, no analgesic effects of sweet taste or chewing were found. However, when sex was taken into account statistically significant differences between boys and girls emerged. In the blood-draw sub-study, analyses of the effects of sweet taste and chewing, when examined separately by sex, revealed a significant interaction in males only on the FPS. Post-hoc tests showed that in males in the Sweet+chew group, those who chewed sweetened gum had significantly increased pain ratings compared with males in the Chew group, who chewed unsweetened gum. The Sweet+chew group was not significantly different from controls. It is unclear how to interpret this. It would appear that sweet taste is canceling an analgesic effect of chewing. In females the significant main effect of chewing, with the Chew group reporting higher pain ratings on the FPS suggests that chewing increases pain. Again, it is unclear what to make of this.

In the vaccination sub-study in males there were significant interactions of sweet taste and chewing on both the CAS and the FPS. Only on the CAS did post-hoc tests reveal that males in the Chew group, who chewed unsweetened gum, had decreased pain
ratings compared with males in the Sweet+chew group, who chewed sweetened gum. In females, no significant main effects or interactions were found. Thus, an apparent analgesic effect of chewing was seen in boys, on the FPS in the blood-draw study and on the CAS in the vaccination study. This effect appeared to be reversed by sweet taste since the Sweet+chew group, which received both sweet taste and chewing interventions, had higher pain ratings than the chew group only. This result was contrary to the hypothesis that both stimuli would interact, possibly synergistically, to reduce pain. Although this underlines a possible analgesic effect for chewing in males, it mainly emphasizes the importance of sex differences when examining the possible analgesic effects of sweet taste and chewing in children. It is unclear why sweet taste should cancel the analgesic effect of chewing, and why this was only seen in boys. Future studies on sweet taste and chewing must stratify the sample for the sex of the participants, as in studies done with adults (Mercer & Holder, 1997).

In summary, the consistent male and female patterns appear to account for the three-factor interactions seen between sex and sweet taste and chewing. The interactions and main effects are also consistent with the robust pattern of responses seen across the two sub-studies over both CAS and FPS. Because the effects of sweet taste and chewing were small, statistically significant effects were not found consistently for sweet taste, chewing or their interaction across both response variables.

The primary hypothesis that sweet taste would reduce pain ratings was not confirmed. Four main factors could account for the lack of clear analgesic effects for sweet taste.

First, the painful stimulus may have been inadequate for the purposes of this study. Unlike an experimental pain stimulus such as the cold-pressor test, used by Miller
et al. (1994). This study used clinical pain stimuli. The acute tissue injury caused by vaccination and venepuncture needles/fingerprick lancets may have been too transient a pain stimulus for the effects of sweet taste to be properly evaluated by self-report. Alternatively, needles may have been very anxiety-provoking stimuli, compared with a cold water arm bath to which the children assented in Miller et al.'s study (1994). A number of children participating in this study did not want the vaccinations or blood-draws. Nonetheless, subjects in this study were trained to rate pain intensity and pain anxiety separately on two scales and appeared to do so consistently.

Second, it is possible that the sweet gum was not sweet enough for analgesia to have occurred. The sweetness of the 2g of gum chewed for 1 minute was rated by adults subjects as at least as sweet as a 15% sucrose solution. The chewing gum however may not have been of equal sweetness as a sugar solution held in the mouth for 1 minute (or more) as used in the Miller et al. study. It is possible that children chewing gum in the present study did not experience an equivalent and maximal sweetness throughout the duration of stimulus administration, unlike Miller et al. subjects' may have (1994).

A third possibility for the lack of analgesia may be related to the quality of the sweet taste itself. It is possible that the chewing gum, although sufficiently sweet, was not pleasant. Some authors (Mercer & Holder, 1997) have suggested that the analgesic effect of sweet taste may not be due strictly to sweetness but rather to the pleasantness or palatability of the stimulus (i.e. its hedonic qualities). In the present case the gum may have been sweet enough but not pleasant enough. In both studies a number of children complained about the taste of the gum. In the hospital setting only 22 out of the 47 children who received sweet gum rated it as "very good" or "good". The number of children who truly enjoyed the gum may actually have been smaller due to possible
reporting bias by children eager to please the experimenter. Thus if the analgesic effect of sweet taste is a function of the pleasantness of the stimulus it is not surprising that there was no analgesia. The sweet solution used by Miller et al. was a 24% sucrose solution (1994). In the present study, chewing gum approximately as sweet was used, however it was sweetened with aspartame. The sweetness of aspartame may not have been pleasant but rather disagreeable. As reported in the results section of the blood-draw study, in children who rated the gum as “Very good” or “Good” there was still no evidence for sweet taste analgesia. The group receiving sweet taste and chewing interventions still had higher pain ratings than children receiving only the chew intervention. Because this analysis was done with a restricted sample of only 22 subjects, it is unclear whether or not a low palatability rating of the gum could account for the lack of sweet taste analgesia.

Fourth, preference for sweet taste declines with age (Desor et al., 1977). The absence of an analgesic effect for sweet taste in the present studies may be related to the age of the participants. In a study by Miller et al. (1994), in which a sweet tasting solution was found to be analgesic the subjects were a younger sample than the children in the present study (notably all were under 11 years of age). In the blood-draw study, the mean age of children was 10±1.2 (Mean±SD) years. However results were no different in the vaccination study in which subjects were younger, ranging in age from 9 to 11 years (Mean±SD: 9.64±0.44 years), which was the upper two thirds of ages of subjects in Miller et al.’s study (1994).

The primary hypothesis that chewing would reduce pain ratings was also not supported.

As with sweet taste, it is possible that the painful stimulus was too transient for the effects of chewing to be properly evaluated by self-report. Another reason chewing did
not produce analgesia in the present experiments may be due to a minimum required rate of chewing which was not achieved. In piloting it was found that of the five children observed all chewed at a rate greater than 30 chews per minute (generally over 60 times per minute). This rate exceeded the 40 chews per minute rate which in cats caused activation of serotoninergic descending neurons (Rueter et al., 1997). Sucking a pacifier in infants was also analgesic only when a rate of 30 sucks per minute was exceeded (Blass & Watt, 1999). Since a minimal chewing rate was not imposed on children, it is possible though unlikely that girls in both schools and PTC did not chew at a sufficiently high rate for chewing induced analgesia to occur. It is also possible that a higher chewing rate than 30 chews per minute is required in children to activate analgesia but this appears unlikely.

The reason for a lack of effect may simply be that serotoninergic circuits that are activated by chewing in cats were not activated in children chewing gum. It is not known whether or not descending serotoninergic analgesic circuits can be activated this way in humans. The analgesic effects of rhythmic oromotor activity have been demonstrated in infants in a few instances as described above. This type of analgesia may be developmentally limited to infancy, a time when oromotor activity such as sucking is of immediate relevance to survival.

Finally, it is possible that the social desirability of appearing “tough”, as discussed below, affected children’s self-reports of pain intensity and affect.

**Correlations**

Other authors have reported high correlations between measures of pain and fear in children between the ages of 3 and 17 years undergoing needle procedures (Fradet et
Such correlations have led to the suggestion that the acute cutaneous pain of needle punctures, anticipatory anxiety and pain behaviour are relatively unitary phenomena (Fradet et al., 1990). Although we observed strong correlations between pain intensity and pain unpleasantness ratings (see Results above), correlations between baseline affect (a measure of anticipatory anxiety) and pain intensity or unpleasantness varied by sub-study and by sex of participants (see Tables 3 and 5).

In girls in both studies, baseline affect ratings were significantly correlated with post-pain affect ratings. In the vaccination study however, there was no such correlation in boys (see Tables 3 and 5). The influence of the experimental settings is one factor that may account for the sex differences in correlations of pre- and post-pain affect ratings. The lack of correlation between pain intensity and affect ratings in boys may be due to social influences from their peers in the group setting in which they were vaccinated. Sex biases in pain reporting have been documented in pre-adolescents. Aho and Erickson (1985) suggested that the 7-year-olds in their study might have been more susceptible to reporting bias caused by a group setting. The social desirability of appearing “tough” may have influenced children reporting their baseline anxiety ratings in the school/vaccination setting where they were able to monitor each other’s answers to some extent. Specifically, in the school/vaccination setting, children were seated next to one another while they gave baseline affect ratings at one of three contiguous stations and children appeared to be comparing their answers. In some cases, they exchanged knowing or quizzical glances with one another or gave particular intonations in their answers. Boys in particular may have altered their baseline ratings to appear brave in front of their peers that could account for the lack of correlation in boys. This finding is consistent with a study on firsts, third and fifth graders who reported that they would be less likely to express pain in
front of a peer than in presence of a parent or when alone. Girls reported that they would be significantly more likely to express pain than boys would. The most commonly cited reason for this reluctance to show their feelings of physical pain was the expectation of a negative interpersonal reaction (Zeman & Garber, 1996). In the blood-draw sub-study where children were interviewed individually by the RA with a parent and technologist present, sex differences in correlations were not seen. This is consistent with the absence of peers and thus of peer associated social pressure in the Pediatric Test Center.

Age and BSA correlations with pain intensity and affect ratings in the blood-draw study differed significantly from previous research. Although age was significantly correlated with pain ratings, we did not find as Goodenough et al. (1997b) had that BSA predicted pain severity scores at least as well as chronological age did. This may be due to the restricted range of children’s ages and BSAs in the present study compared to the children in Goodenough et al.’s study (who ranged in age from 3 to 17yrs) (1997b). Pain intensity did not vary as a function of the anatomical index of BSA but did vary as a function of age. Arts et al. (1994) speculated that the influence of age on self-report and behavioural pain scales could be in part the result of activation of more nociceptors (summatng both spatially and temporally) in smaller bodies.

**Limitations**

Future studies of this nature should consider using behavioural measures in conjunction with self-report ratings of pain. One study on brief behavioural interventions for acute pain reported inconsistencies between self-report and physiological measures of responses to acute experimental pain (Bruehl et al., 1993). Subjects instructed in relaxation techniques displayed beneficial physiological changes without significant
psychological changes. The participants trained in the intervention did not have altered pain or emotion ratings relative to controls. As the authors suggest, this highlights the importance of assessing pain concurrently across modalities (e.g. psychological and physiological). Although self-report is considered the gold standard for pain assessment because of the intrinsically subjective nature of pain, physiological correlates of pain may have their place in similar studies in the future.

**Implications and Summary**

This study has emphasized the complexity of examining the effects of sweet taste and chewing on pain self-report in children. This attempt to use physiological stimuli to activate endogenous pain modulatory pathways was unsuccessful. However, it raised interesting questions regarding the interaction of sex with the effects of sweet taste and chewing on pain.

Sweet taste is analgesic in human neonates as outlined in Chapter 1. In older infants a statistically significant but only clinically modest analgesic effect of sweet taste has been shown (Barr et al., 1995: Barr et al., 1994). The extent to which sweet taste is still analgesic in pre-adolescent children and under which conditions such an effect may be elicited is unclear.

Despite the absence of clear analgesic effects of sweet taste and chewing, the present study provides a framework for guiding future research. It underlines a number of variables that need to be studied in the future, including the measures used to assess pain, the palatability of the stimuli and most notably the sex of the participants. In addition, the results of the music analogy training suggest that pre-adolescent children can be taught to use CAS and FPS scales to rate stimuli on distinct sensory and affective dimensions.
Considering the lack of analgesic effects of sweet taste in this study and their presence in the study of Miller et al. (1994), a follow-up study would be appropriate. It would be interesting to include an additional group in which subjects would receive a stimulus of equal salience to a sweet solution but which would not be hedonically positive (e.g., quinine solution). The increased pain threshold Miller et al. (1994) reported may have been the result of distraction from the pain simply by a salient stimulus. It may not have been an opioid-mediated analgesic effect from the sweet solution, since the participants kept the sweet solution in their mouths throughout the pain task. One test of the potential involvement of opioids in sweet taste analgesia would require a delay between the end of sweet taste administration and the painful stimulus administration. As discussed above, sweet taste may have a biphasic effect comprised of a stimulus bound phase from the saliency of the stimulus taste, followed by a post-stimulus possibly opioid-mediated effect. Thus, after a two-minute delay, once the distraction of either quinine or sweet tasting solution had worn off, only the opioid-mediated effect of sweet taste would cause analgesia.

The present research underlines the difficulty of studying the multifaceted experiences of pain and analgesia. Using ostensibly mundane stimuli such as sweet taste and chewing belies the complicated phenomena under investigation. The inherent complexity of the central nervous system poses a challenge for understanding the effects of stimuli on pain without resorting to gross oversimplifications and erroneous attributions of causality.
Reference List


Fig 1: Effect of Sweet taste and Chewing on CAS pain intensity ratings. Blood-draw data: Males only

CAS rating by Condition

Fig 2: Effect of Sweet taste and Chewing on FPS pain affect ratings. Blood-draw data: Males only

FPS rating by Condition

Note: Control group = not chew not sweet. Sweet group = sweet not chew. Chew group = not sweet chew. Sweet+Chew group = sweet chew.
Fig 3: Effect of Sweet taste and Chewing on CAS pain intensity ratings. Blood-draw data: Females only

CAS rating by Condition

Fig 4: Effect of Sweet taste and Chewing on FPS pain affect ratings. Blood-draw data: Females only

FPS rating by Condition

Note: Control group = not chew not sweet. Sweet group = sweet not chew. Chew group = not sweet chew. Sweet+Chew group = sweet chew.
Fig 5: Effect of Sweet taste and Chewing on CAS pain intensity ratings. Blood-draw data: Across sex

CAS ratings by Condition

---

![Graph showing CAS ratings by Condition with sweet and not sweet conditions.]

Note: Control group = not chew not sweet. Sweet group = sweet not chew. Chew group = not sweet chew. Sweet+Chew group = sweet chew.
Fig 7: Effect of Sweet taste and Chewing on CAS pain intensity ratings. Vaccination data: Males only

![Graph showing CAS rating by Condition](image_url)

Note: Control group = not chew not sweet. Sweet group = sweet not chew. Chew group = not sweet chew. Sweet+Chew group = sweet chew.

Fig 8: Effect of Sweet taste and Chewing on FPS pain affect ratings. Vaccination data: Males only

![Graph showing FPS rating by Condition](image_url)
Fig 9: Effect of Sweet taste and Chewing on CAS pain intensity ratings.
Vaccination data: Females only

Fig 10: Effect of Sweet taste and Chewing on FPS pain affect ratings.
Vaccination data: Females only

Note: Control group = not chew not sweet. Sweet group = sweet not chew. Chew group = not sweet chew. Sweet+Chew group = sweet chew.
Fig 11: Effect of Sweet taste and Chewing on CAS pain intensity ratings. Vaccination data: Across sex

CAS ratings by Condition

Fig 12: Effect of Sweet taste and Chewing on FPS pain affect ratings. Vaccination data: Across sex

FPS ratings by Condition

Note: Control group = not chew not sweet. Sweet group = sweet not chew. Chew group = not sweet chew. Sweet+Chew group = sweet chew.
Appendix A: Coloured Anologue Scale (CAS)

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McGill, 1991

MOST PAIN

NO PAIN

Compliments of CHILDREN'S TYLENOL®
cotaminophen
1-800-265-7323
Appendix B: Faces Pain Scale (FPS)
### Appendix C: Sample data collection form

<table>
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Appendix D: Script for music analogy training in hospital

PTC Music analogy 1: Quiet Music First
In a few minutes you are going to have a blood-draw down the hall. Right before the needle I will ask you how you feel and then after I will ask you how it was. I’m going to ask you to answer using two scales. Here are the two scales (show). First we’re going to practice using the scales together so listen carefully.

Practice analogy: Loud/Pleasant
Imagine I’m listening to music on the radio. I hear a song that is playing very loud.
Q1: If someone asks me to show them: how loud the music?~, I move the line into this part of the scale: Because this end of the scale says: Very Loud Music. The other end of the scale is for when there is no music. This same song that is playing is a song that I like, and it makes me feel good (it’s pleasant). Q2: If someone asks me to point to the face that shows how I feel when I hear that song I point to this face because it shows someone who feels good. The other faces show people who feel bad. OK, now you get a chance to practice on your own.

Analogy 1: Quiet/Unpleasant
Imagine that you are listening to music on the radio.
You hear a song that is playing very softly.
Q1: Can you show me how loud the music is playing? (CAS). This same song that is playing is music that you don’t like and it makes you feel bad. Q2: Can you point to the face that shows me how you feel when you hear this music? (Faces). Perfect!

Analogy 2: Loud/Pleasant
Now I’d like you to imagine again that you are listening to music on the radio. However, this time you hear a different song. and it’s playing very loud. Q1: Can you show me how loud the music is playing? (CAS). This same song that is playing is music that you like and it makes you feel good. Q2: Can you point to the face that shows me how you feel when you hear this music? (Faces). Perfect! Now let’s go back to the test centre where I am going to ask you some similar questions. I want you to answer the questions honestly. Tell me how you really feel. There is no right or wrong answer. Also I’m going to give
you a piece of chewing gum to chew before the needle. I’ll let you know when you can start chewing and I’ll ask you to spit the gum out at some point. Also please don’t swallow the gum! Do you have any questions?

**PTC Music analogy 2: Loud Music First**

PTC Music analogy 2 was identical to PTC Music analogy 1 except that the Quiet/Unpleasant analogy was presented as the Practice analogy followed by Loud/Pleasant and Quiet/Unpleasant analogies.
Appendix E: Research assistant’s script for blood-draw

Baseline: J’aimerai que tu me montres la face qui indique comment tu te sens maintenant (FACES).

Child chews gum then child spits gum

S’il te plait crache ta gomme.

J’ai trois questions pour toi:

1. J’aimerais que tu m’indiques combien de douleur tu as eu durant la piqûre (CAS) (combien cela a fait mal)
2. Et sur cette autre échelle montre moi la face qui indique comment tu t’es senti durant la piqûre (Faces).
3. Et finalement j’aimerai que tu me montres ce que tu as pensé de la gomme (Gum scale). Excellent! Merci.

Baseline: I’d like you to point to the face that shows me how you feel right now. (FACES)

Child chews gum then child spits gum

Please spit out your gum.

I’ve got three questions for you:

1. I’d like you to show me how much pain you just had during the needle (CAS)
2. And on this second scale I’d like you to show me how you just felt during the needle (FACES).
3. And last of all I’d like you to show me what you thought of the gum (Gum scale). Excellent! Thank you very much.
Appendix F: Letter to parents

1999/10/04

Vaccination, douleur et gomme à mâcher

Cher parent,

Nous aimerions vous inviter ainsi que votre enfant à participer à une étude qui aura pour but de voir si le fait de mâcher de la gomme modifie la douleur associée à la vaccination que votre enfant recevra bientôt. L’intervention est simple. Nous demanderons à votre enfant de mâcher un morceau de gomme à mâcher sucrée ou non-sucrée (fabriqué par la compagnie Gumtech) durant le 1er vaccin contre l’hépatite B le 15 Octobre 1999. Ensuite, nous lui demanderons d’évaluer comment il se sent sur une échelle ressemblant à un thermomètre et sur une échelle de "visages".

Nous ferons une présentation d’une quinzaine de minutes en classe le 14 Octobre pour permettre à votre enfant de se familiariser avec ces deux échelles. Nous désirons vous assurer que la participation de votre enfant à cette étude ne changera pas la façon dont il recevra sa vaccination. S’il y a quelque chose, notre étude pourrait rendre la procédure complète plus plaisante.

Nous aimerions vous remercier de prendre quelques minutes pour considérer ce projet de recherche. Si vous aviez des questions, vous pouvez nous contactez au (514) 934-4400 poste 3285 ou au (514) 934-4314. Vous pouvez nous laisser un message avec vos coordonnées et le meilleur moment pour vous rejoindre et nous nous ferons un plaisir de vous rappeler.

Nous vous serions reconnaissants de nous retourner pour demain la formule de consentement. Nous vous remercions de votre intérêt pour ce projet de recherche et de votre coopération.

Sincèrement,

Dr Ronald G. Barr
Maxim Lewkowski
Appendix G: Consent form

Analgesie en réponse à un stimulus sensoriel chez les enfants

Département de pédiatrie

Investigateurs : Ronald G. Barr, MDCM, FRCP(C)
Simon N. Young, PhD

Cher Parent,

Nous aimerions que votre fils ou fille participe à une étude pour déterminer si le fait de mâcher de la gomme sucrée ou non sucrée affecte l'expérience douloureuse durant les immunisations ou lors d'un prélèvement sanguin. Nous aimerions évaluer cela en demandant à votre enfant d'indiquer comment forte et désagréable est la douleur en utilisant deux échelles simples qui utilisent des couleurs et des dessins de visages. Nous enseignerez à votre enfant comment utiliser ces échelles avant la procédure. Nous demanderons aussi à votre enfant de mâcher de la gomme durant différentes étapes de la procédure. Le moment où il (elle) mâchera de la gomme et s'il s'agira d'une gomme sucrée seront déterminés au hasard. Toute la procédure, incluant la mastication de la gomme, prend moins de dix minutes.

Si vous acceptez que votre fils ou fille participe à ce projet, votre coopération sera requise de ces façons:

En nous permettant de vous demander ainsi qu'à votre enfant quelques questions pour déterminer la raison de la procédure, l'expérience antérieure avec les aiguilles, et la langue préférée;

En nous permettant de donner à votre enfant un morceau de gomme à mâcher qu'il mâchera pendant environ deux à trois minutes.

En nous permettant de demander à votre enfant de décrire la force et le caractère désagréable de la procédure en utilisant des échelles de "couleur" et de "visages".

Tous les résultats seront confidentiels. Tous les documents portant des noms seront gardés en sûreté par l'investigateur principal; tous les autres rapports porteront seulement un numéro de code. Le nom de votre fille ou fils sera retiré de tous les documents de la recherche dès que tous les résultats de l'étude seront recueillis. Si vous le désirez, vous pouvez être présent pour n'importe quelle étape de cette étude.

Risques et malaises

Recevoir une immunisation ou faire un prélèvement sanguin ne fait pas partie de ce projet de recherche. Toutes les autres procédures décrites ci-dessus font partie du projet de recherche.
recherche. Nous ne connaissons aucun risque ou malaise lié aux procédures du projet de recherche. Si votre enfant souhaite se coucher à n'importe quelle étape de la procédure, il ne recevra pas de gomme à mâcher pour éviter toute ingestion accidentelle.

Bénéfices potentiels

La participation à cette étude peut, ou peut ne pas avoir de bénéfice direct pour votre fils ou fille. S'il y a quelque chose, l'expérience douloureuse pourrait être réduite par la participation à cette étude. De plus, les résultats de cette étude peuvent démontrer que la douleur provoquée par l'immunisation ou par un prélèvement sanguin peut être réduite d'une façon relativement simple ce qui pourrait être utile à d'autres.

Consentement

J'ai expliqué en entier à ______________________ (parent[s]) la nature et le but des procédures décrites ci-dessus et les risques qui sont impliqués dans leur exécution. J'ai demandé aux parents s'ils ont des questions en rapport avec les procédures et ai répondu à leurs questions au meilleur de mes connaissances.

_______________________________
Assistant de recherche / Signature de l'associé Date

J'ai été pleinement informé(e) des procédures ci-dessus, avec leurs effets bénéfiques possibles, risques et conséquences. Je donne la permission que mon fils ou ma fille participe à cette étude. Je sais que Dr Ronald G. Barr ou ses associés (tél : 514-934-4400, poste 3285) vont être disponibles pour répondre aux questions que je peux avoir. Je comprends que je suis libre de retirer ce consentement et d'interrompre la participation à ce projet en tout temps sans affecter les soins de mon fils ou ma fille.

_____________________________
Signature du parent ( ou du tuteur ) Date

_____________________________
Signature du patient(e) ( âgé(e) de 7 ans ou plus ) Date

____________________________
Signature du participant Date
Appendix H: Script for music analogy training presented in school

Demain (après la fin de semaine) vous allez avoir votre dernière piqûre. Moi et quelques autres personnes vont vous poser des questions. On va vous demander de donner une réponse à nos questions sur deux échelles. Je vais vous laisser regarder une de ces échelles (distribute CAS and copies of Faces). Si tout le monde a vu les échelles je vais vous demander de les passer vers le devant de la classe. Maintenant on va se pratiquer à utiliser ces échelles. Vous avez tous trois feuilles de papier: une blanche, une rose et une verte. Écrivez vos noms sur chaque feuille dans l’espace indiqué.

Practise round: Feuille Blanche: Musique forte, mais que tu aimes.
Maintenant prenez la feuille blanche sur le bord avec le long triangle marqué “musique très forte” et “pas de musique” dessus. Imaginez que vous entendez de la musique à la radio. Vous entendez une chanson qui joue très fort. Q1. Si je demande à Jodi d’indiquer “Comment forte est la musique? (CAS)”, elle dessine une ligne avec un crayon. sur le dessin ICI: Elle le dessine ici parce que ce bord dit: Musique Très Forte. L’autre coté de l’échelle est pour quand il n’y a pas de musique. Maintenant tournez la page. Cette même musique qui joue est une chanson que Jodi aime, et qui la fait sentir bien (elle est agréable). Q2. Si je demande à Jodi d’encercler la face sur la feuille qui montre comment elle se sens quand elle entend cette musique. Jodi encerle la première face, celle ci, parce qu’elle à l’air de quelqu’un qui se sent bien. Les autres faces montrent des gens qui se sentent mal. Maintenant c’est à vous de vous pratiquer seuls.

Feuille Rose: Musique basse, mais que tu n’aimes pas.
Maintenant prenez la feuille rose sur le bord avec le long triangle marqué “musique très forte” et “pas de musique” dessus. Imaginez que vous entendez de la musique à la radio. Vous entendez une chanson qui joue très légèrement (pas forte). Q1. Indiquez, en faisant une ligne avec un crayon, sur le dessin: Comment forte est la musique? (CAS) Ne tournez pas la page. Maintenant tournez la page. Cette même musique qui joue est une chanson que tu n’aimes pas du tout, et qui te fait sentir mal (elle est très désagréable). Q2. Encerclez une face sur la feuille qui montre comment tu te sens quand tu entends cette musique.

Feuille Verte: Musique forte, mais que tu aimes
Maintenant prenez la feuille verte sur le bord avec le long triangle marqué “musique très forte” et “pas de musique” dessus. Imaginez à nouveau que vous entendez de la musique à la radio. Cette fois ci vous entendez une chanson qui joue très fort

Q1. Indiquez, en faisant une ligne avec un crayon sur le dessin: Comment forte est la musique? (CAS). Maintenant tournez la page. Cette même musique qui joue est une chanson que tu aimes, et qui te fait sentir bien (elle est agréable). Q2. Encerclez une face sur la feuille qui montre comment tu te sens quand tu entends cette musique. Est-Ce Que tout le monde à terminé? Très bien alors passez vos feuilles vers l’avant de la classe.

Demain (ou Lundi) nous et quelques autres personnes allons vous poser quelques questions similaires. On veut que vous répondez honnêtement. Dites-nous comment vous vous sentez pour vrai. Il n’y a pas de bonnes ou de mauvaises réponses. On veut savoir exactement comment vous vous sentez. Aussi pour ceux d’entre vous qui participeront à l’expérience demain (ou Lundi), on vous donnera de la gomme à mâcher sucrée ou non. On vous dira quand vous pouvez commencer à la mâcher et quand vous devez la cracher dans la poubelle. S’il vous plait ne l’avalez pas! Avez-vous des questions? Merci et à demain (ou Lundi).
Appendix I: Research assistant’s script for vaccination study

Baseline
Te souviens-tu de ce qu’on avais discute en classe hier? Maintenant on va se pratiquer une dernière fois. Imagine que tu entends de la musique qui:
- joue très légèrement: Montre-moi comment forte est la musique? (slide cursor up and down). Excellent.
- cette même musique qui joue est une chanson que tu n’aimes pas du tout, et qui te fait sentir mal (elle est très désagréable): Montre moi la face qui indique comment tu te sens quand tu entends cette musique? Parfait.

Imagine que tu entends de la musique qui
- joue très fort: Montre-moi comment forte est la musique? (slide cursor up and down). Excellent.
- cette même musique qui joue est une chanson que tu aimes, et qui te fait sentir bien (elle est agréable): Montre moi la face qui indique comment tu te sens quand tu entends cette musique? Parfait.
OK là oublie la musique et montre moi comment tu te sens maintenant? (Faces)
Super.
Là je vais te demander de regarder ce sablier et mâcher de la gomme

Attendre (tu mâcheras après la vaccination).
Quand le sable sera termine de couler tu lèveras la main et ça sera a ton tour d’aller voir une infirmière. OK?
Begin chewing or wait for 1_min. then proceed to vacc. station..

Vaccination
→ Piqûre ←
-Bonjour NOM. Tick-off participant # on sheet
- J’ai deux questions pour toi:
  1. J’aimerais que tu m’indiques combien de douleur tu as eu? (CAS) (combien cela a fait mal)
  2. Et sur cette autre échelle montre moi comment te sens-tu? (Faces) Excellent! Merci beaucoup.
Remind not to chew gum until told. Direct to post-table. Keep track of whether they: cry, read a book, try to negotiate. smile. ask questions etc...