F2 Intercross

Definition

The second-generation descendants of a cross of two contrasting populations (e.g., inbred strains). The offspring of the cross (i.e., F1 hybrids) are sib-mated to produce F2 hybrids, in which homologous recombination has “shuffled” the genomes of the progenitors in a unique manner. F2 hybrids from inbred strain progenitors are useful for quantitative trait locus (QTL) mapping.

Cross-References

▶ Quantitative Trait Locus Mapping

Fabry’s Disease

Definition

Visual pain scale of seven faces now tested in older adults as well as children.

Cross-References

▶ Cancer Pain, Assessment in the Cognitively Impaired

Facet Denervation

Cross-References

▶ Facet Joint Procedures for Chronic Back Pain

Facet Joint

Definition

Facet is a flat, platelike surface that acts as part of a joint, as seen in the vertebrae of the spine and in the subtalar joint of the ankle. Each vertebra has two superior and two inferior facets. Facet joints are small stabilizing synovial joints located between and behind adjacent vertebrae.

Cross-References

▶ Chronic Back Pain and Spinal Instability
▶ Chronic Low Back Pain: Definitions and Diagnosis
▶ Facet Joint Pain
▶ Pain Treatment: Spinal Nerve Blocks
Facet Joint Injection

▶ Facet Joint Procedures for Chronic Back Pain

Facet Joint Pain

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Synonyms

Facet syndrome; Sciatica; Zygapophysial joint pain

Definition

Although the intervertebral joint has long been known to be a common generator of low back pain and leg pain, the facet joint has been proposed as another potential focus of degenerative pathology that can produce similar symptoms. Structurally analogous to joints in the extremities, the facet joint has the capacity to degenerate over time and cause pain through the same mechanisms that are at play in osteoarthritis of the hip or the knee. This pain can be “felt” by the patient in the area of the facet, producing low back pain, or it can potentially be referred to other parts of the body through the activation of adjacent nociceptive fibers. Radiofrequency, cryoneuroablation, and chemical neurolysis are all possible treatment modalities for lumbar facet syndrome (Wheeler and May 2010). Although a “facet syndrome” including a component of sciatica was initially proposed, stimulation of the nerve supply to facet joints in live subjects has shown reproducible patterns of pain that are limited to the low back, flank, abdomen, and buttock. Many studies have claimed a benefit from treatment of low back pain through interventions aimed at disrupting the primary afferents supplying the facet joint, but the handful of randomized clinical trials of these interventions has generally failed to demonstrate any benefit beyond placebo (Carette et al. 1991; Leclaire et al. 2001; Lilius et al. 1989; Slipman 2003). These studies have been criticized, however, and their generally negative results may stem from poor patient selection and improper selection of therapeutic target. In 2009, a panel of experts in interventional therapies and surgery recommended against the use of facet joint steroid injections as a treatment for lower back pain. Their decision was based upon insufficient evidence from previously conducted studies (Chou et al. 2009b). Although rates of use for facet joint injections increased by 231% from 1994 to 2001, these therapies have shown to only improve short-term pain management (Friedly et al. 2007; Chou et al. 2009a).

Characteristics

Anatomical Considerations

Ghormley is credited with coining the phrase the “facet syndrome” in 1933 (Ghormley 1933). In his seminal article, he noted that facet joints were the only “true” joints in the spinal column, meaning that they contain a complete joint capsule with a clear synovial membrane and hyaline cartilage at the articular surface. Such true joints are termed zygapophysial joints and exist in all the typical weight-bearing places affected by osteoarthritis such as the hip, the knee, and the ankle. He conjectured and offered histopathological evidence that these joints degenerate over time like their counterparts in the extremities. He theorized that this process could produce a syndrome of low back pain, scoliosis, and sciatica, perhaps induced by rotatory strain of the lumbosacral region.

Detailed anatomical studies of the nerve supply of facet joints have provided the blueprint for testing and treating the “facet syndrome.” Each joint is innervated by spinal nerves from
the adjacent and superior vertebral level on the ipsilateral side (Bogduk and Long 1979; Maldjian et al. 1998; Mooney and Robertson 1976). Arising from the dorsal root ganglion, the medial branch of the posterior ramus passes through a notch at the base of the transverse process. Twigs are given off to the facet joint at the same level before the nerve descends inferiorly, giving off muscular and cutaneous branches, as well as a branch to the superior aspect of the facet joint one vertebral level below. Bogduk and Long published the most detailed anatomical study of these relationships, and proposed calling the branches comprising this dual nerve supply the proximal and distal zygapophysial nerves (Bogduk and Long 1979). These same authors recognized variability at L5–S1 mandated by the absence of transverse processes at this level, and noted the medial branch of the posterior ramus of L5 passes through a groove between the sacral ala and the root of the superior articular process of the sacrum. The key points from this anatomical study were that denervation of a facet joint would require a lesion of the medial branch of the posterior ramus at the same vertebral level and the level above, and that a denervation procedure directed at the facet joint proper might result in an incomplete lesion.

**Provocative Studies**

The first report of nervous stimulation of facet joints that induced back and leg pain was by Hirsch et al. in 1963 (Hirsch et al. 1963). The first systematic analysis of referred lumbar facet joint pain was written by Mooney and Robertson in 1975 (Mooney and Robertson 1976). These authors studied five normal subjects and 15 patients with low back pain, and reported a nonspecific pattern of pain referral to the flank, buttock, and the leg upon injection of 5% hypertonic saline into the facet joint. An important discrepancy was noted between normal and low back pain patients in that the latter complained of more frequent and more widespread patterns of pain referral. The only reports of induced pain in a sciatic distribution came from the low back pain cohort. These authors also related their results with fluoroscopically guided anesthetic injections, and offered a detailed description of the procedure, which served as a model for future studies. Due to difficulty in locating the precise vertebral level of the pain generator, injections at three lumbar levels were advocated and injections were directed into the facet joint proper. The facet joint, as the target of treatment, has been used by many clinicians and in many studies ever since, but this approach has come under criticism by some, who maintain that a more efficacious target of anesthetization or neurotomy is the medial branch of the posterior ramus (Bogduk and Long 1979).

The technique of Mooney and Robertson was applied (McCall et al. 1979) to six healthy individuals who received fluoroscopically guided injections of 6% hypertonic saline into lumbar facet joints of L1–2 and L4–5. They noted several important findings. L1–2 injections reproduced pain to the adjacent lower back, flank, and groin. L4–5 injections produced pain in the adjacent lower back, buttock, groin, and lateral thigh. There was significant overlap in the distribution of the patterns of referred pain, even though the facet joints selected were three levels apart, and there was no patient that complained of pain below the mid-thigh.

Provocative studies have shown fairly clearly that stimulation of the sensory nerves around facet joints can induce pain, and that this stimulation can reproducibly generate pain that is referred to other parts of the body. It is still unclear to what extent this induced pain has a relationship to the clinical entity of low back pain in the general population. The paucity of provocative evidence for the induction of referred leg upon stimulation of facet joints in control populations casts some doubt on the sciatic component of the alleged “facet syndrome.” The lack of dermatomal specificity for referred pain from facet joint stimulation may reflect the dual level innervation, and contribute to the difficulty in localization of the potential pain-generating level.
Randomized Clinical Trials

There have been multiple studies of treatments for facet joint pain including both anesthetic and steroid injections and radiofrequency nerve ablations. These studies vary greatly in their selection criteria and reported results. For example, reported efficacy of facet joint steroid injection ranges from 10 % to 63 % (Carette et al. 1991). The vast majority of these studies are retrospective case series. These divergent results likely stem from variable selection criteria, variable technique and target selection, variable follow-up, and variable criteria for a successful treatment. As such, they are very difficult to interpret. One review of these studies found “sparse evidence” to support the use of interventional techniques in the treatment of facet joint pain, and called for more randomized clinical trials (Slipman 2003).

Four peer-reviewed randomized clinical trials for the treatment of low back pain through facet joint procedures have been published, and the conclusion from three out of four of these studies was that no treatment has demonstrated any benefit beyond placebo (Carette et al. 1991; Leclaire et al. 2001; Lilius et al. 1989; van Kleef et al. 1999). There are criticisms of each study, however, which could have significantly affected results, and these criticisms are discussed below.

In 1989, Lilius et al. (Lilius 1989) randomized 109 patients with low back pain to receive injections of cortisone, local anesthetic, or saline into two facet joints. Patients were examined at 1 hour, 2 weeks, and 6 weeks, and also filled out a questionnaire regarding work performance and pain level at 3 months. Seventy percent of patients experienced initial pain relief and 36 % of patients reported continued benefit at 3 months. These results were irrespective of the contents of the injection. The major flaw in this study was that there were no selection criteria beyond low back pain to ensure that the facet joints were the pain generators in these patients. Another criticism was that the facet joint was used as the therapeutic target and not the medial branch of the posterior ramus.

In 1991, Carette et al. (Carette 1991) randomized 97 patients who reported >50 % immediate relief from low back pain following local anesthetic injection into facet joints, both at L4–5 and at L5–S1, to receive either steroid injections or saline injections. They followed the technique described by Mooney and Robertson (i.e., fluoroscopic guidance using contrast to localize the facet joint and injection into the facet joint proper). Patients were assessed immediately following the procedure and at 1-, 3-, and 6-month follow-up intervals. They found that 11 patients in the steroid group and 5 patients in the saline group had prolonged relief from the injections. The difference was not statistically significant. A post-hoc analysis of the subgroup of patients who claimed >90 % relief from the initial anesthetic injections yielded similar results. As mentioned previously, the target selection according to the technique of Mooney and Robertson has been criticized. It is also notable that their results approached significance ($p = 0.19$), begging the question of whether their study was simply underpowered.

In 1999, van Kleef et al. (van Kleef 1999) randomized 31 patients selected for >50 % relief from facet nerve block to receive radiofrequency nerve ablation or sham treatment. These authors targeted the medial branch of the posterior ramus according to the description of Bogduk and Long. Patients were assessed immediately after the procedure and at 1-, 3-, 6-, and 12-month intervals. Although initial analysis of their patient population showed no statistically significant benefit of radiofrequency ablation over placebo, a post-hoc analysis of the patients that reported the most relief from screening anesthetic injections demonstrated a benefit from the procedure. The authors concluded that this subpopulation of patients were the true sufferers of facet joint pain and that these patients, when properly selected, would benefit from radiofrequency neurotomy.

In 2001, Leclaire et al. (Leclaire 2001) randomized 70 patients selected for “significant” relief of low back pain after two level anesthetic injections. The target selected was the facet joint itself. Patients were assessed at 4 weeks and at
12 weeks using two measures of functional inability and one pain scale. Although one of the functional assessments showed a small but statistically significant improvement in the treatment group at 4 weeks, there were no statistically significant differences in the other functional assessment or the pain assessment at 4 weeks, or in any of the outcome measures at 12 weeks. The authors concluded that beyond a mild transient reduction in functional disability, radiofrequency facet joint neurotomy had no proven benefit in the treatment of low back pain. No post-hoc analysis of the patients who were most relieved by the selecting anesthetic injections was done. This study was criticized for its vague selection criteria and for its use of the facet joint as a target (Dreyfuss et al. 2002).

In 2005, Fuchs et al. (Fuchs 2005) randomized 60 patients suffering from chronic lumbar pain in a blind-observer clinical trial to evaluate the therapeutic results of intra-articular sodium hyaluronate (SH) injections versus glucocorticoid (TA) injections. The patients were divided into two groups to be treated with either 10-mg SH or 10-mg TA. The injections were delivered per facet joint bilaterally (from L3-S1) on a weekly basis. Level of pain was determined by the Visual Analog Scale (VAS), and life quality was determined by the Roland Morris questionnaire, Oswestry Disability questionnaire, Low Back Outcome Score and the Short Form 36 (SF-36) questionnaire. Throughout the 180-day trial period, both groups of patients demonstrated increased positive results in pain relief and quality of life. As for long-term results (>6 months), the sodium hyaluronate injections were potentially more beneficial for patients when compared to the glucocorticoid injection therapy (Fuchs et al. 2005).

While the existence of a “facet syndrome” that includes sciatica seems unlikely, a syndrome of low back pain caused by degenerative changes in the facet joints seems plausible. Provocative studies of sensory nerves to facet joints, as well as the close anatomical association between the nervous supply to the facet joint and the dorsal root ganglion, provide evidence of a pattern of referred pain to areas as distant as the buttocks and inguinal region. The prevalence of this entity within the vast population of patients with low back pain remains unknown.

Randomized clinical trials have failed to demonstrate convincing data to justify facet joint steroid injections or radiofrequency neurotomy within the populations of patients studied, but these results could easily be the result of improper patient selection. In the absence of a reliable radiographic diagnostic tool, more stringent screening criteria are required before these procedures should be dismissed. The cut-off of >50 % pain relief after a single session of anesthetic injections used by the studies reviewed may be too liberal and/or too unreliable. One interesting study probed this issue. Starting with 176 patients with low back pain, 47 were selected that reported a “definite” or “complete” response after facet block with a short-acting anesthetic. When this cohort was brought back for a confirmatory block 2 weeks later, only 15 % reported >50 % response (Schwarzer 1994). Facet joint degeneration may thus be a relatively rare cause of low back pain. Perhaps, anesthetic injections are simply not a reliable screening tool. Also, the difficulty to locate the exact site of the pain is a common problem in injection therapy (Fuchs et al. 2005). Another explanation for the negative results from clinical trials may lie in target selection. It has yet to be determined whether the facet capsule or the medial branch of the posterior ramus is preferred. Only randomized trials of steroid injections or ablation procedures that use more stringent selection criteria and compare results using different therapeutic targets will answer these questions.

References


**Facet Joint Procedures for Chronic Back Pain**

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**Synonyms**
Facet denervation; facet joint injection; facet rhizolysis; medial branch block; median branch block; radiofrequency ablation; zygapophyseal joint injection; zygapophysial joint injection

**Characteristics**
Zygapophyseal (facet) joints are synovial diarthroses and are present from C1 to S1, inclusive. These joints allow for articular motion in the posterior spinal column and are innervated by medial branch of the primary posterior ramus of the segmental spinal nerves. Each articular process receives innervation from a spinal nerve, so each joint, comprised of two articular processes, is innervated by two medial branches (Fig. 1).

The medial branch is primarily sensory to the joint and surrounding structures and is innervated richly with nociceptive fibers. Numerous pain-mediating neurotransmitters (e.g., bradykinin, substance P, and neuropeptide Y) are also found in these neurons (Morinaga et al. 1996). These nerves are also motor to the multifidus muscles, and multifidus EMG studies have been used to validate the results of radiofrequency medial branch denervation (Dreyfuss et al. 2000).

Initially, the approach to treating facet arthropathy-related pain was limited to surgical excision and/or stabilization. It is difficult to assess the results of the surgical approaches to facet arthropathy, as patients do not uniformly have diagnostic procedures first, and the surgical treatment is almost always a part of another surgical procedure (e.g., fusion, laminectomy).
Joint injections with local anesthetic and steroid are still popular in many practices, but these injections have not been demonstrated to be reliably diagnostic (due to potential epidural spread of injectate) or of any prolonged therapeutic value (Dreyfuss and Dreyer 2003). Numerous prospective, double-blinded, randomized controlled trials have shown these injections to be no better than placebo in the treatment of chronic back and neck pain (Barnsley et al. 1994; Carette et al. 1991). There have been no significant studies since these indicate that there is a role for intraarticular steroid injections.

Fluoroscopically guided diagnostic medial branch blocks anesthetize the facet joint selectively and are used to provide prognostic information for radiofrequency medial branch denervation. They are not intended for prolonged analgesia. Generally, a two-block paradigm is used: one injection of short-acting local anesthetic and one of long-acting anesthetic (Lord et al. 1995) (Figs. 2 and 3). Some authors have attempted to use ultrasound as guidance for this procedure, and in ideal settings, it is possible that there may be a role. However, in clinical practice, body habitus and the inability to detect intravascular injections or perform injections at more than one site at a time will remain significant barriers (Rauch et al. 2009).

There has been debate regarding the exact interpretation of these blocks, fueled by the problems inherent in attempting to make an objective diagnosis in a subjective disorder (i.e., pain). Much of this debate has focused on the test characteristics of the procedure and uses terms such as “placebo response” and “false positive”
Unfortunately, these terms are misleading in this sense. A subject may have an unanticipated response to an injection, but if an active treatment is used, by definition, that response is not a placebo response. Moreover, it is inappropriate to use the term “false positive” in this situation, as there is no gold standard test with which to compare the results.

These studies do not take into account the analgesic effect that simultaneously anesthetizing the multifidus muscle has, which may account for the prolonged duration of some subjects’ responses. Therefore, since this field deals with subjective responses, most operators use a somewhat more liberal interpretation of the results of diagnostic medial branch blocks and allow for prolonged concordant responses (i.e., both responses more prolonged than would be expected solely due to the local anesthetic but of duration proportional to the anticipated duration). In addition, multifidus is denervated by the radiofrequency denervation procedure, but there are no long-term sequelae (Dreyfuss et al. 2009).

Once the diagnosis of painful facet arthropathy is made, radiofrequency facet denervation is the minimally invasive treatment of choice. This technique has been used over the last four decades and has advantages in the treatment of facet arthropathy over other neurolytic techniques, such as chemodenervation or cryotherapy. As the technology and techniques have improved, prospective studies have demonstrated efficacy in select groups, although there has been some lack of uniformity among these results (Dreyfuss et al. 2002; Niemisto et al. 2003; Slipman et al. 2003). There has been one prospective study of lumbar radiofrequency medial branch denervation that produced negative (non-difference from placebo) results (van Wijk et al. 2005). However, the technique in this study was non-standard, and other authors in this field have challenged the results, as the technique was likely to miss the target nerve (Bogduk 2006). Since then, several studies have demonstrated positive results, though there is still a need for a large, multicenter, prospective, randomized trial (Nath et al. 2008; Burnham et al. 2009).

The technique involved in radiofrequency facet denervation is similar to that of medial branch blocks, inasmuch as the instrument is placed in proximity to the medial branches innervating a joint, as opposed to entering the joint itself (Lau et al. 2004). However, instead of using plain needles, special cannulae are used. These are coated with heat-shrink Polyethylene Terephthalate (PET) tubing in order to insulate most of the needle. This focuses the release of radiofrequency energy on the active tip, which leads to a focused, reproducible lesion. When positioned appropriately, this lesion includes the medial branch, while limiting collateral damage to surrounding structures. As a result of this precision, the risk of adverse events is exceedingly low (Kornick et al. 2004). The safety profile is one of the features that make this procedure an attractive alternative in the treatment of this common disorder.
The desired outcome in this procedure is the focal denervation of the joints in which the patient’s back pain was relieved upon performance of diagnostic medial branch blocks. This does not treat the underlying arthropathy but reduces the painful limitation to mobility that it causes. The nature of radiofrequency denervation does allow for regrowth of the medial branch nerve. Therefore, the procedure may require repetitive treatments over time. Longer-term cohorts and studies of repeated intervention indicate that the clinical results of the procedure last approximately 12 months, which is consistent with a period of denervation, followed by regrowth of the medial branch nerve (Tomé-Bermejo et al. 2011; Rambaransingh et al. 2010). Since the denervation procedure does not address comorbidities, such as myofascial pain, post-denervation physical therapy may be used to extend the benefits of the procedure, to include relief of myofascial pain and associated loss of range of motion.

Due to the increasing use of this procedure in the United States (Friedly et al. 2007), insurers have sought to limit its availability by placing stringent requirements on patients with facetogenic pain prior to approving radiofrequency medial branch denervation (Noridian Local Coverage Determination; United Health Care Medical Policy). While the data supporting this procedure are imperfect, there is only one significant negative study, which used a nonstandard technique. The weight of evidence for the positive symptomatic and functional effects of radiofrequency medial branch denervation is far greater than for most analgesic interventional procedures. It remains to be seen whether this useful, safe procedure will continue to be available to those who most benefit from its use.

References


Facet Rhizolysis

Facet Syndrome

- Facet Joint Pain

Facial Ganglion Neuralgia

- Geniculate Neuralgia

Facial Pain

Definition

Facial pain is identified by its location, usually excluding tic douloureux.

Cross-References

- Pain Treatment, Motor Cortex Stimulation

Facial Pain Associated with Disorders of the Cranium

- Headache from Cranial Bone

Facilitative Tucking

Definition

A caregiver uses his/her hands to swaddle an infant by placing a hand on the infant’s head and feet while providing flexion and containment.

Facet Rhizolysis

- Facet Joint Procedures for Chronic Back Pain

Cross-References

- Acute Pain Management in Infants
Factor Loading

Definition

Factor analysis is a statistical procedure that groups together variables that share common variance. Variables that “load” on the same factor are presumed to reflect a similar underlying process.

Cross-References

▶ Psychology of Pain, Self-Efficacy

Factors Associated with Low Back Pain

Definition

Clinical syndrome characterized by back or lower extremity pain or both following surgery for decompression of neural elements in the lower back.

Cross-References

▶ Low Back Pain, Epidemiology

Failed Back

Definition

Clinical syndrome characterized by back or lower extremity pain or both following surgery for decompression of neural elements in the lower back.

Cross-References

▶ Pain Treatment: Spinal Cord Stimulation

Failed Back Surgery Syndrome

Definition

Failed back surgery syndrome is axial or radicular pain persisting after surgical approaches to relieve the pain. It is also known as failed back syndrome.

Cross-References

▶ Central Nervous System Stimulation for Pain
▶ Dorsal Root Ganglionectomy and Dorsal Rhizotomy

False Affirmative Rate

Definition

False affirmative rate is the probability of response “A” when event B has occurred.

Familial Adenomatous Polyposis

Synonyms

FAP

Definition

An inherited disease which is characterized by the formation of numerous polyps on the inside walls of the colon and rectum. The FAP disease is associated with a 100 % risk for developing colorectal cancer.

Cross-References

▶ NSAIDs and Cancer

Familial Amyloid Polyneuropathy (FAP)

Definition

Failed back surgery syndrome is axial or radicular pain persisting after surgical approaches to relieve the pain. It is also known as failed back syndrome.

Cross-References

▶ Hereditary Neuropathies
Familial Factors

- Impact of Familial Factors on Children’s Chronic Pain

Family-Centered Care

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Synonyms

Family-centered theory; Patient-centered care

Definition

What Is Family-Centered Care?
The practice of pediatrics focuses on the health of a child. The experience of pediatric care, however, is not isolated to the child; the experience impacts the whole family. In fact, a bidirectional relationship exists whereby efforts to provide holistic care to a child necessarily involve accounting for relevant contextual factors. Context includes elements internal to the child, such as developmental level, as well as external to the child, such as familial influences. The method and degree to which this relationship is embraced in the care setting is the focus of an approach called family-centered care.

While the central tenants of family-centered care may be practiced to varying degrees around the world, most of the published literature on this topic has originated from the United States and United Kingdom in the last two decades. Definitions articulate an approach to decision making and information sharing, captured most powerfully in one word, partnership. Together, healthcare practitioners, patient, and family navigate each step along the care pathway with intention and respect.

A framework for family-centered care in pediatrics, originally described by Shelton in 1987, includes the following nine elements:
- Recognizing the family as a constant in the child’s life

Cross-References

- Migraine, Pathophysiology

Familial Polyposis Coli

Definition

People with this syndrome have massive numbers of colonic polyps and almost invariably develop cancer of the colon.

Cross-References

- NSAIDs and Their Indications

Family Environment

- Impact of Familial Factors on Children’s Chronic Pain

Familial Hemiplegic Migraine

Definition

Familial hemiplegic migraine is an inherited form of migraine with aura in which patients experience weakness and other neurological disturbances as their aura.

Cross-References

- Migraine, Pathophysiology
Facilitating parent-professional collaboration at all levels of health care
Honoring the racial, ethnic, cultural, and socioeconomic diversity of families
Recognizing family strengths and individuality and respecting different methods of coping
Sharing complete and unbiased information with families on a continuous basis
Encouraging and facilitating family-to-family support and networking
Responding to child and family developmental needs as part of healthcare practices
Adopting policies and practices that provide families with emotional and financial support
Designing health care that is flexible, culturally competent, and responsive to family needs

According to the Institute for Family-Centered Care, established in 1992 in the USA, the summary themes include: respect and dignity; information sharing; participation; and collaboration (Committee on Hospital Care. American Academy of Pediatrics & Institute for Patient-and Family-Centered Care, 2003).

Characteristics

Pediatric Pain and Family-Centered Care
Pain in children is complex. Yet, the fundamental human right to pain care drives the field to further scientific study and the individual practitioner to prevent and alleviate children’s pain. From parents’ perspective, data show that the top two (among 36) issues of priority for their children admitted to an acute care setting were “Find out what is wrong with my child” and “taking care of my child’s pain if it is relevant.” And yet, pain presented the greatest discrepancy between priority and level of satisfaction (Ammentorp 2005). Through the alignment of science and humanity, the greatest possible impact on the short- and long-term consequences of poorly treated or untreated pain in children can be realized. Therein lays the synergy of a family-centered care approach to improve a child’s experience with pain; a partnership of evidence-based health care and the expertise of self-report or parents’ knowledge of their child.

Clinical: A Call to Action
A commitment to partner along the clinical care continuum particularly illustrates the powerful opportunity, including assessment, planning, intervention, and evaluation. First, the cornerstone of effective pain care is assessment. Evolution of study has led to an iterative set of developmental-age specific tools to assess the intensity of children’s pain. However, healthcare practitioners are not treating an intensity number, they are treating a person. Thus, it becomes essential to engage a parent to share and observe behavioral cues noticed in their child, or honor an adolescent’s self-report of the quality, location, duration, and aggravating and relieving factors (Reid et al. 1995). From the outset, it must be noted that communication is foundational and continuous (Garland and Kenny 2006). Thus, eliminating language disparity via routine and readily accessible interpreter services is critical (Guerrero et al. 2010). This exchange informs planning for pain care and draws upon the critical component of respect. The well-recognized, positive effects of an interdisciplinary approach to pain care match the collaborative model of family-centered care (Huth et al. 2003; Shields et al. 2006; Simons et al. 2001). This is an opportunity to welcome and optimize a family’s strengths and an individual child’s coping style. The importance of optimizing patient and parent participation and coping has been clearly demonstrated, such as in a cohort of adolescents with sickle cell disease (Mitchell 2007). A partnership to share information allows for unbiased presentation of evidence-based interventions and nonjudgmental discussion. It becomes essential to recognize that all parties may hold different elements of the care at a premium, including evaluation of the risk and benefit of the pain experience itself, as well as the interventions and goals.
Education: Empowering Advocates
Efforts to enhance awareness and knowledge of children’s pain through education can give new voice to all. Education offers a link to close the gap between the prevalence of undertreated or untreated pain in children and the lack of timely, effective interventions to prevent or alleviate that pain. In its 2011 publication titled “Relieving Pain in America,” the Institute of Medicine cites education as a foundational endeavor to transform care (IOM 2011). The aim of educational activities may focus on expectations and current evidence of pain care to inform a shared mental model, yet importantly also focus on the benefit of each member’s individual expertise. In other words, to recognize that a healthcare provider has the responsibility to contribute expertise in current evidence-based treatment options, while a parent has the responsibility to contribute expertise in their child’s context and current experience. Such messaging again emphasizes communication as key; there is support for anyone to speak up and advocate on behalf of a child, including truly creating space for and hearing the voice of a parent.

Research: Data to Improve Outcomes
In recent years, further collaboration between the scientific community and the healthcare consumer offers another example of, and opportunity for, a powerful partnership (MacKean et al. 2005). For example, the Patient-Centered Outcomes Research Institute (PCORI) is an independent, nonprofit organization in the USA created to contribute specifically to shared, informed decision making by patients, families, and healthcare providers. Patients play a central role to define research priorities, contribute to the direction of clinical queries, and gain access to results. Another example is the Patient Reported Outcomes Measurement Information System (PROMIS), which is funded by the US National Institutes of Health (NIH). These measures become the tools of scientific study to inform the effectiveness of interventions and have already invested in pain as a focal area. Specifically in pediatrics, this entity has made available validated tools to assess pain interference and intensity, as well as focusing on areas of physical function, emotional distress, fatigue, and peer relationships. Thus, research offers an arena not only for patient and parent participation, but also for collaboration to define priorities for study and new forums in which to share results.

What Do the Data Show with Regard to Family-Centered Care?
A systematic review (Shields et al. 2008) underscored the paucity of solid quantitative research on the effectiveness of family-centered care. Qualitative studies, and subsequent quantitative efforts, have shown the impact of family-centered care to (Bamm and Rosenbaum 2008; Kuo 2012):
• Improve patient outcomes
• Improve patient and family satisfaction
• Improve healthcare professionals’ satisfaction
• Decrease cost
• Improve utilization of resources in health care

In line with these results, leading professional and safety organizations have endorsed family-centered care. In the USA, for example, the Institute of Medicine (IOM) identified family-centered care as one of the six attributes of high-quality health care (IOM 1999, 2001), and the Joint Commission incorporated a bill of rights that included patient comfort and that active involvement of patients and families is a strong strategy to ensure patient safety.

Summary
The synergy between family-centered care and the practice of pediatric pain medicine is undeniable. The data available assert its value to the extent that it is sanctioned as a primary safety and quality strategy. Yet, the challenge remains in the translation of a philosophy in approach to bedside practice. For some healthcare settings this would present a complete interdisciplinary
paradigm shift, while at the same time offer a tremendous opportunity for culture change in treating pain in children. It is possible. First, the system must define the professional standards, set expectations for behavior, and create the space for a rich partnership. Then, the system must maintain accountability to that model, including individual practitioner responsibility. In time, a culture will emerge in which the partnership of family-centered care will transform the experience of a child in pain.

References


Family-Centered Care, Approach and Basis

Definition

The American Academy of Pediatrics Committee on Hospital Care and the Institute for Family-Centered Care issued a joint policy statement in which they defined terms as follows: “Family-centered care is an approach to health care that shapes health care policies, programs, facility design, and day-to-day interactions among patients, families, physicians, and other health care professionals.” Further, “Family-centered care in pediatrics is based on the understanding that the family is the child’s primary source of strength and support and that the child’s and family’s perspectives and information are important in clinical decision making.”
References


Family-Centered Care, Objective

Definition

Care directed at improving the health and well-being of the family and its members by assessing the family health needs and identifying potential obstacles.

Cross-References

▶ Chronic Pain in Children, Physical Medicine and Rehabilitation

Family-centered Theory

▶ Family-Centered Care

FAP

▶ Familial Adenomatous Polyposis

Fascia Iliaca Compartment Block

Definition

Injection via needle or catheter of local anesthetic deep to the fascia lata and iliaca medial to the anterior superior iliac spine and inferior to the inguinal ligament.

Fasciculus Cuneatus

Definition

The lateral bundle of nerves in the dorsal column referred to as the cuneate fasciculus, which terminates in the cuneate nucleus just off the dorsal midline in the caudal medulla.

Cross-References

▶ Postsynaptic Dorsal Column Projection, Anatomical Organization

Fasciculus Gracilis

Definition

The medial bundle nerves in the dorsal column referred to as the fasciculus gracilis, which terminates in the gracile nucleus in the dorsal midline of the caudal medulla.

Cross-References

▶ Postsynaptic Dorsal Column Projection, Anatomical Organization

Fast-Track Surgery

▶ Postoperative Pain, Importance of Mobilization
Fatigue

Definition

Fatigue is a decrement of response seen with repeated stimulation and is a prominent attribute of nociceptors and other primary afferents.

Cross-References

► Pain in Humans, Electrical Stimulation (Skin, Muscle, and Viscera)
► Polymodal Nociceptors, Heat Transduction

FCA

► Freund’s Complete Adjuvant

FCA-Induced Arthritis

Definition

This is the same as CFA (Complete Freund’s Adjuvant)-induced Arthritis. An experimental model of inducing rheumatoid arthritis by injecting a suspension of killed mycobacteria (Freund’s complete adjuvant, FCA) into various tissues in rats. The classical model involves injection of high doses into the tail base which produces multiple joint arthritis (polyarthritis) accompanied by widespread lesions of skin and other organs. A modified method uses low-dose local injections around a joint to produce unilateral single joint arthritis.

Cross-References

► Opioids and Inflammatory Pain

FCE

► Functional Capacity Evaluation

Fear and Pain

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Synonyms

Fear of movement/(re)injury; Kinesiophobia; Pain-related anxiety; Pain-related fear

Definition

► Fear of pain is a general term used to describe several forms of fear with respect to pain. Depending on the anticipated source of threat, the content of fear of pain varies considerably. For example, fear of pain can be directed toward the occurrence or continuation of pain, toward physical activity, or toward the induction of (re) injury or physical harm. A more specific fear of pain concerns ► fear of movement/(re)injury, which is the specific fear that physical activity will cause (re)injury. Synonymously, ► kinesiophobia is defined as “an excessive,
irrational, and debilitating fear of physical movement and activity resulting from a feeling of vulnerability to painful injury or re-injury” (Kori et al. 1990; Lundberg et al. 2006).

Characteristics

In recent years, chronic pain has no longer been conceptualized as purely a medical problem but rather as a complex biopsychosocial phenomenon in which the relationship among impairments, pain, and disability is weak. In chronic pain patients, anxiety disorders frequently co-occur, indicating that patients with persistent musculoskeletal pain fear a variety of situations that are not essentially related to pain (Asmundson and Katz 2009; Asmundson et al. 2004; Gatchel et al. 2007). Besides the finding that chronic pain patients seem to suffer more frequently from anxiety symptoms, fear and anxiety are often an integral part of the chronic pain problem. The experience of pain can be characterized by psychophysiological (e.g., muscle reactivity), cognitive (e.g., worry), and behavioral (e.g., escape and avoidance) responses, showing similarities with responses regarding fear and anxiety (Leeuw et al. 2007; Vlaeyen and Linton 2000).

There are multiple pathways by which pain-related fear mediates disability, namely, through escape and avoidance behaviors, through interference with cognitive functioning, through reduced opportunities to correct the erroneous underlying cognitions guiding the avoidance behaviors, and through detrimental effects of long-lasting avoidance on various physiological systems (Crombez et al. 1999; Gheldof et al. 2006; Turk and Wilson 2010). Empirical findings support the notion that fear of pain is a significant contributor to the chronification and maintenance of chronic pain syndromes (Hirsh et al. 2008; Turk and Wilson 2010; Vlaeyen and Linton 2000).

Fear and Anxiety

In the literature describing fear of pain, the concepts of fear and anxiety are often used interchangeably. Despite the fact that these concepts are substantially related, some differences can be distinguished (Asmundson et al. 2004; Leeuw et al. 2007; Sylvers et al. 2011).

Fear is the emotional expression of the fight-flight response, which is the immediate readiness of the body to respond to an event that is perceived as dangerous or threatening. Fear is therefore a present-oriented state that is designed to protect the individual from the perceived immediate threat. Anxiety, however, is a cognitive-affective state that is rather future oriented. It tends to occur in the anticipation of a dangerous or threatening event and is therefore more indefinite and uncertain in nature. Instead of initiating the fight-flight response as in case of fear, the state of anxiety seems to facilitate and stimulate the fight-flight response only in case the threatening event occurs. Both in fear and anxiety, cognitive, physiological, and behavioral dimensions of responses can be distinguished. Physiologically, fear and anxiety responses are characterized by the activation of the sympathetic nervous system, designed to increase the likelihood of survival by promoting escape from or protection against the perceived threat. In anxiety, these physiological responses are less present than in fear. The cognitive element, relatively more present in anxiety, is more narrowed in anxiety and directed in such a way that a source of threat, when present, will be detected. Fear, on the other hand, comprises thoughts of danger, threat, or death, through which the attention toward the threat is advanced, while irrelevant distracters are ignored and the initiation of action is stimulated. On a behavioral level, anxiety guides motivation to engage in preventative and avoidance behaviors, while fear motivates to engage in defensive behaviors. Despite the definition of pain-related fear, both fear and anxiety are distinct processes that contribute significantly to chronic pain (Asmundson et al. 2004).

Hierarchy of Fear

Besides the important distinction between fear and anxiety in chronic pain, understanding about the hierarchical nature of fear and anxiety is also an important consideration. The hierarchical structure of anxiety is displayed in Fig. 1.
Fundamental Fears
According to the expectancy theory (Reiss and McNally 1985), most fears can be derived from one of three more fundamental fears or sensitivities: (1) fear of anxiety symptoms (anxiety sensitivity), (2) fear of negative evaluation (social evaluation sensitivity), and (3) fear of illness/injury (injury/illness sensitivity). Anxiety sensitivity refers to the fear of anxiety symptoms arising from the belief that anxiety has harmful somatic, psychological, and social consequences. Social evaluation sensitivity reflects anxiety and distress that is associated with expectations that others will have negative evaluations about oneself and with avoidance of evaluative situations. Finally, injury/illness sensitivity refers to fear concerning injury, illness, or death. These fundamental fears are quite distinct from each other and comprise stimuli that are considered to be essentially aversive to most people (Asmundson et al. 2000; Vlaeyen 2003).

Common Fears: Fear of Pain
Common fears (such as spider phobia, agoraphobia, fear of pain) arise as the result of an interaction between the fundamental fears and learning experiences and can thus be logically derived from these three fundamental fears. In contrast to fundamental fears, they do not refer to a wide variety of stimuli and are not essentially considered to be aversive to most people. Due to fear of anxiety, causing one to fear the symptoms that are associated with anxiety, a common fear about a particular situation easily arises when in the concerning situation anxiety symptoms are expected or likely to be experienced. In essence, anxiety sensitivity can be considered as a vulnerability factor that exacerbates the development and maintenance of common fears, the same holding for injury sensitivity and social evaluation sensitivity (Asmundson et al. 2000).

In chronic low back pain, fear of pain is a common fear that can be derived from the fundamental fear of anxiety symptoms (anxiety sensitivity). When someone who is highly anxiety sensitive expects to encounter anxiety symptoms during the experience of pain, fear of pain will likely develop (Asmundson et al. 2000; Ocañez et al. 2010). However, Keogh and Asmundson (2004) argue that it is more reasonable to assume that fear of pain is related to injury/illness sensitivity, which is also supported by Van Cleef et al. (2006). Fear of pain is still a relatively general construct. Fear of pain can be directed at pain sensations as well as activities and situations that are associated with pain. In chronic low back pain patients, one of the more specific forms of fear of pain is fear of movement/(re)injury, which is the specific fear that physical activity will cause (re)injury (Vlaeyen and Crombez 1999).

Specific Fears: Fear of Movement/(Re)Injury
A number of CLBP patients believe that performance of certain activities may induce or promote pain and (re)injury. Beliefs concerning harmful consequences of activities lead to fear
of movement/(re)injury and consequently to the avoidance of these activities, although medical indications for this behavioral pattern of avoidance are lacking. Despite the fact that in acute pain the avoidance of daily activities may be adaptive in facilitating healing and recovery, avoidance behavior is no longer necessary for recovery in chronic pain (Leeuw et al. 2007; Vlaeyen and Linton 2000).

Cognitive Behavioral Models
A cognitive behavioral model of chronic low back pain has been proposed, which emphasizes the crucial importance of the role of fear of movement/(re)injury and avoidance behavior in chronic low back pain patients (Vlaeyen 2003; Vlaeyen and Linton 2000). According to the model, two opposing behavioral responses may occur in response to acute pain: “confrontation” and “avoidance.” A gradual confrontation and resumption of daily activities despite pain is considered as an adaptive response that eventually leads to the reduction of fear, the encouragement of physical recovery, and functional rehabilitation. In contrast, a catastrophic interpretation of pain is considered to be a maladaptive response, which initiates a vicious circle in which fear of movement/(re)injury and the subsequent avoidance of activities augment functional disability and the pain experience by means of hypervigilance, depression, and disuse. Substantial support for this cognitive behavioral model and the role of the specific fear of movement/(re)injury has been found (Leeuw et al. 2007; Vlaeyen and Linton 2000).

In addition to this cognitive behavioral model, Asmundson et al. (2004) propose to update the model by integrating the concept of anxiety in addition to fear, referring to this as the fear-anxiety-avoidance model (Fig. 2).

This model states that catastrophizing about pain produces fear of pain, designed to protect the individual from the perceived immediate threat. This fear of pain in turn might promote pain-related anxiety. Pain-producing stimuli result through pain-related fear in escape and protecting behaviors aimed at reducing pain intensity. These behaviors in turn strengthen erroneous beliefs about pain, increase catastrophizing, and further enhance pain-related fear. The addition of an anxiety-related pathway to the pathway of pain-related fear provides a more accurate explanation for the fact that chronic pain interferes with one’s daily life. In the anticipation, rather than in the presence of pain and/or injury, anxiety is evoked, leading to an increased attention (hypervigilance) for evidence of potential pain or injury. This hypervigilance and psychical responses may interact with memories and may promote misinterpretations of harmless stimuli as impending danger of pain or injury. Behaviorally, anxiety results in avoidance and preventative behaviors, increasing disability and disuse (Asmundson et al. 2004).
Recently, the sequential relationships between changes in pain catastrophizing, subsequent fear and avoidance, and functional outcomes such as disability or return to work were examined using a prospective design (Wideman et al. 2009). Although overall changes in pain catastrophizing and fear of movement were predictive for return to work, no evidence was found that early changes in catastrophizing were associated with late changes in fear of movement. These findings suggest that both components might independently influence disability. At present, new cognitive behavioral models regarding pain-related fear are evolving, focusing on behavior in context. Fear of pain might result in diverse behaviors depending on the current goal context, and likewise, seemingly similar behaviors may be driven by dissimilar motivational strategies (Van Damme et al. 2008; Vlaeyen et al. 2009).

**Other Objects of Fear in Pain**

Morley and Eccleston (2004) propose the existence of a range of “feared objects” in chronic pain, because of the overwhelming threat value of pain and three associated capacities to (1) interrupt, (2) interfere, and (3) impact on one’s identity. Many potential fears arise because of the ability of pain to threaten the whole range of a person’s existence. Interruption is established because the immediate pain experience interrupts behavior and influences the person’s cognitive functioning (e.g., thoughts about possible harm). Interference is visible in the diminished accomplishment of daily functional activities. Finally, when repeated interference occurs to a degree that it concerns major goals, a threat to the identity is instigated. As chronic pain interferes with current tasks, plans, and goals, the person’s perspective of oneself is changed, both with respect to the future and the past. Fear and anxiety are likely to occur when the goals and the identity of a person are threatened (Morley 2008).

**Assessment of Fear of Pain**

Several measurements of fear of pain are available (for an overview see McNeil and Vowles 2004). Anxiety sensitivity can be measured by the 16-item Anxiety Sensitivity Index (ASI) (Peterson and Reiss 1987), measuring the degree to which people are concerned about the possible negative consequences of anxiety symptoms. Injury/illness sensitivity can be measured with the corresponding subscale of the sensitivity index (Taylor 1993). Fear of pain can be measured by, for example, the Pain Anxiety Symptoms Scale (PASS) (McCracken and Dhingra 2002; McCracken et al. 1993), designed to assess pain-specific fearful appraisals, cognitive symptoms of anxiety, physiological symptoms of anxiety, and escape and avoidance behavior. Another way to assess pain-related fear is by means of the Fear of Pain Questionnaire (FPQ), a self-report measure utilized in clinical as well as in nonclinical populations (McNeil and Rainwater 1998). Fear of movement/(re)injury can best be measured with the 17-item Tampa Scale for Kinesiophobia (TSK; Kori et al. 1990).

**Treatment Implications**

Due to the inextricable binding between fear and (chronic) pain, treatment of chronic pain should aim to focus on these perpetuating factors. In graded exposure in vivo, a hierarchy of fearful activities is established, which leads to disconfirmation of pain beliefs and reduction of fear, thereby promoting recovery of activities and functional abilities (Vlaeyen et al. 2004; Woods and Asmundson 2008). Fear- and anxiety-focused treatments seem to provide promising results in chronic low back pain patients (Bailey et al. 2010; Lohnberg 2007).

**References**


Fear Avoidance

Definition

Fear avoidance is the avoidance of activities in order to prevent injury, reinjury, or exacerbation of any injury or pain. It is a learned behavior to reduce negative pain-related emotions. In this way, pain-related fear can lead to disability, catastrophizing beliefs, hypervigilance to bodily signals, and avoidance behavior.

Cross-References

- Disability
- Fear Avoidance
- Pain
- Psychological Treatment of Pain in Older Populations

Fear of Movement/(Re)Injury

Definition

Fear related to movement and physical activity, inextricably associated with the fear that physical activity will cause pain and (re)injury. Fear of movement is most prominent in patients with chronic pain syndromes.

Cross-References

- Disability, Fear of Movement
- Fear and Pain

Fear of Pain

Definition

Pain-related fear is a general term to describe several forms of fear with respect to pain. Depending on the anticipated source of threat, the content of fear of pain varies considerably. Fear of pain can be directed toward the occurrence or continuation of pain, toward physical activity, or toward the induction of (re)injury or physical harm.

Cross-References

- Disability, Fear of Movement
- Fear and Pain
- Muscle Pain, Fear-Avoidance Model
Fear Reduction Through Exposure In Vivo

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Synonyms
Exposure in vivo; Exposure treatment; Extinction; Graded exposure; Graded exposure in vivo with behavioral experiments

Definition
Exposure in vivo, originally based on extinction of Pavlovian conditioning (Bouton 1988), is currently viewed as a cognitive process during which fear is activated and catastrophic expectations are being challenged and disconfirmed, resulting in reduction of the threat value of the originally fearful stimuli. During graded exposure, special attention goes to the establishment of an individual hierarchy of the pain-related fear stimuli. Exposure in vivo includes activities that are selected based on the fear hierarchy and the idiosyncratic aspects of the fear stimuli.

Characteristics
In order to produce disconfirmations between expectations of pain and harm, the actual pain, and the other consequences of the activity or movement, Philips (1987) was one of the first to argue for repeated, graded, and controlled exposures to such situations. Experimental support for this idea is provided by the match-mismatch model of pain (Rachman and Arntz 1991), which states that people initially tend to overpredict how much pain they will experience, but after some exposures these predictions tend to be corrected to match with the actual experience. Crombez et al. (2002) and Goubert et al. (2002) found a similar pattern in a sample of chronic low back pain patients, who were requested to perform certain physical activities. As predicted, the chronic low back pain patients initially overpredicted pain, but after repetition of the activity, the overprediction was readily corrected. Overpredictions of pain and the negative consequences of pain are more pronounced in individuals reporting increased fear of pain. A number of studies examined the effectiveness of a graded exposure in vivo treatment in reducing pain-related fear, pain catastrophizing, and pain disability in chronic pain patients who were referred for outpatient behavioral rehabilitation (Vlaeyen et al. 2002a, b, c; Vlaeyen et al. 2001; de Jong et al. 2005a, b, 2008, 2012; Leeuw et al. 2008; Linton et al. 2008; Woods and Asmundson 2008). Theses showed improvements in pain-related fear, pain catastrophizing, and pain disability whenever the graded exposure was initiated. Measured with ambulatory activity monitors, the improvements also generalized to increases in physical activity in the home situation (Vlaeyen et al. 2002a). Besides behavioral and cognitive changes, one study in patients with Complex Regional Pain Syndrome (CRPS) even found observed positive changes in edema, skin color, excessive sweating, and motor function disturbances (de Jong et al. 2005a). It seems that graded exposure to painful activities, movements, and/or situations that were previously avoided may indeed be a successful treatment approach for pain patients reporting substantial pain-related fear.

Graded Exposure In Vivo
We suggest that the intervention generally be designed in three steps: cognitive-behavioral assessment, education, and exposure in vivo with behavioral experiments.

Cognitive-Behavioral Assessment
Specific Questionnaires A basic question that may be asked is as follows: “What is the nature of the perceived threat?” The answer is not as simple...
as it seems. Patients may not view their problem as involving fear at all and may simply see inability in performing certain activities due to pain. In addition, the specific nature of pain-related fear varies considerably, making an idiosyncratic approach almost indispensable. Patients may not fear pain itself, but the impending (re)injury it signals: pain is seen as a warning signal for a seriously threatening situation. The list below outlines pain-related fear questionnaires, including sample items:

**Pain and Impairment Relationship Scale (PAIRS):** Riley et al. 1988

“I have to be careful not to do anything that might make my pain worse.”

“All of my problems would be solved if my pain would go away.”

**Survey of Pain Attitudes (SOPA) [Subscale Harm]:** Jensen et al., 1992

Measures of Pain Catastrophizing

**Pain Catastrophizing Scale (PCS):** Sullivan et al. 1995

Rumination: “I keep thinking about how much it hurt.”

Amplification: “I grow afraid that the pain will get worse.”

Helplessness: “There’s nothing I can do to reduce the intensity of the pain.”

**Pain Cognition List (PCL) [Subscale catastrophizing]:** Van Breukelen and Vlaeyen 2005

Cognitive Error Questionnaire (LEFEBVRE 1981)

Vignettes about catastrophizing, overgeneralization, personalization, and selective abstraction: e.g., “You have a painful back problem but have continued to work. Although you got quite a bit done today, you quit work a little early because your back was really hurting. You think to yourself, ‘What a terrible day, it seems like I can’t get anything done’.”

**Coping Strategies Questionnaire (CSQ) [Subscale catastrophizing]:** Rosenstiel and Keefe 1983

“I feel I can’t stand it anymore.”

**Fear-Avoidance Beliefs Questionnaire (FABQ):** Waddell et al. 1993

Fear-avoidance beliefs about work:

“My work might harm my back.”

Fear-avoidance beliefs about physical activity:

“My pain was caused by physical activity.”

**Interview** The semi structured interview is an additional tool to better estimate the role of pain-related fear in the pain problem. It includes information about the antecedents (situational and/or internal), catastrophic (mis)interpretations, and consequences of the pain-related fear. Information is gathered about the assumptions patients make of the association between activities, pain, and (re)injury. Factors that often seem to be associated with the development of fear are the characteristics of pain onset and the ambiguity surrounding the presence or absence of positive findings on medico-diagnostics. Reports about misconceptions and misinterpretations of information can later be used during the educational part of the intervention. Finally, the interview should also clarify whether other problems such as major depression, marital conflicts, or disability claims warrant specific attention before or after treatment.

**Graded Hierarchies** What is the patient actually afraid of? In addition to checklists of daily activities, the presentation of visual materials, such as pictures of stressing activities and...
movements reflecting the full range of situations avoided by the patient, can be quite helpful in the development of graded hierarchies. They start with activities or situations that provoke only mild discomfort and end with those that are beyond the patient’s present abilities. The Photograph Series of Daily Activities uses photographs representing various physical daily activities to be placed along a fear thermometer (Dubbers et al. 2003; Jelinek et al. 2003; Kugler et al. 1999; Leeuw et al. 2007).

**Behavioral Tests** Sometimes, patients find it hard to really estimate the harmfulness of an activity when it has been avoided extensively. For cases in which even pictorial methods (PHODA) do not work, behavioral tests can be introduced. These consist of performing an activity that has been avoided previously, while performance indices (e.g., time, distance, number of repetitions) are measured. Target behaviors can be derived from PHODA items, and in most cases the behavioral tests can be considered as a variant of the exercise tolerance test described by Fordyce (Fordyce 1976).

**Education** One of the major goals of the educational section is to increase the willingness of patients to finally engage in activities they avoided for a long time. The aim is to correct the misinterpretations and misconceptions that occurred early on during the development of the pain-related fear. The educational section is more than just reassuring that there are no specific physical abnormalities. Unambiguously educating the patient in a way that the patient views his or her pain as a common condition that can be self-managed, rather than a serious disease or condition that needs careful protection, is a useful first step. It can be explained to patients that they may have probably overestimated the value of diagnostic tests and that in symptom-free people similar abnormalities can also be found.

**Graded Exposure In Vivo with Behavioral Experiments**

**Graded Exposure In Vivo** As firsthand evidence of actually experiencing oneself behaving differently is far more convincing than rational argument, the most essential step consists of graded exposure to the situations the fearful patient has identified as “dangerous” or “threatening.” The patient is encouraged to engage in these fearful activities as much as possible, until disconfirmation has occurred and anxiety levels have decreased. If the rating has decreased significantly, the therapist may consider moving on to the next item of the hierarchy. Each activity or movement is first modeled by the therapist. His presence, initially acting as a safety signal to promote more exposures, is gradually withdrawn to facilitate independence and to create contexts that mimic those of the home situation (Vlaeyen et al. 2012).

**Behavioral Experiments** The graded exposure to fear-eliciting activities can be carried out in the form of a behavioral experiment in which a collaborative empiricism is the bottom line. The essence of a behavioral experiment is that the patient performs an activity to challenge the validity of his catastrophic assumptions and misinterpretations. These assumptions take the form of “If ... then ...” statements and are empirically tested in such a behavioral experiment.

**Generalization and Maintenance of Change** Exposure to physical activities is not likely to result in a fundamental change in the belief of the pain patient that certain movements are harmful or painful (Goubert et al. 2002). More likely, the patient will learn that the movements involved in the exposure treatment are less harmful or painful than anticipated. In other words, during successful exposure, exceptions to the rule are learned, rather than there being a fundamental change of that rule. Generalization and maintenance can be enhanced by the following measures. First, exposure to the full spectrum of contexts and natural settings in which fear has been experienced is required. Second, during the exposure, it is best that stimuli be varied as much as possible. Third, expanded-spaced, rather than a massed exposure, is preferred (Vlaeyen et al. 2012).
References


**Fear-Anxiety-Avoidance Model**

**Definition**

The Fear-Anxiety-Avoidance Model states that catastrophic misinterpretations in response to acute pain can lead to fear of pain and subsequently to pain-related anxiety. Fear urges the escape from the pain stimulus, while anxiety in anticipation of pain or threat urges avoidance of those situations. As a result of this, a self-perpetuating cycle develops in which subsequent avoidance of activities augments functional disability, depression, and decreased physical fitness, thereby further advancing chronicity.

**Cross-References**

▶ Fear and Pain

**Fear-Avoidance**

▶ Disability, Fear of Movement

**Feasible**

**Definition**

The simple, economic, and easy application of a measure

**Cross-References**

▶ Pain Assessment in Neonates

**Feedback Control of Pain**

**Definition**

Ascending nociceptive signals activate supraspinal mechanisms (e.g., an inhibitory brainstem-spinal pathway) that suppress spinal/trigeminal nociceptive transmission.
Female Sex Steroid Hormones and Pain

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Introduction

It widely understood that females are disproportionately affected by pain syndromes when compared to their male counterparts. This clinical skew is notable in conditions such as migraine headache, temporomandibular joint disorder (TMJD), irritable bowel syndrome (IBS), and fibromyalgia (Unruh 1996). In addition to the higher prevalence of females with pain conditions, there have been reports of cyclical patterns of pain onset and severity (Martin 2009). This disparity in pain experience has resulted in a significant body of research comparing gender-specific physiological differences. Most experimental pain studies suggest that females are more sensitive to pain than males, although there are inconsistencies in the literature (Martin 2009; Fillingim et al. 2009). Consequently, researchers have focused on female biology, specifically the menstrual cycle, to untangle this important clinical and biological conundrum. The two main female sex steroid hormones, progesterone and estradiol, are thought to influence pain processing through alteration of a variety of neural mechanisms.

Characteristics

Pain Perception in Healthy Females over the Menstrual Cycle

Animal models have allowed for improved mechanistic understanding of the central effects of progesterone and estradiol; however, differences in the physiology of the ovarian cycle between species causes difficulty in extrapolating some of these findings to humans. In rodents, these hormones have been implicated in a variety of pain-related pathways including the gamma-aminobutyric acid (GABA), glutamate, opioid, and dopamine systems. Thus, estradiol appears to mediate inflammatory responses, increase opioidergic tone, and promote reuptake of glutamate, while progesterone is thought to alter GABAergic inhibitory activity by increasing binding affinity through its metabolite allopregnanolone. Certainly, in rodents there is a notable cyclical trend toward greater pain sensitivity in the proestrus phase, a time that is characterized by dramatic fluctuations of progesterone and estradiol. However, researchers have also observed increased sensitivity at other
points including estrus, metestrus, and diestrus (Reviewed in Martin 2009). In humans, results are more difficult to interpret. A number of factors contribute to this problem, not least the different definitions and methods of verification of the menstrual cycle phases (Sherman and LeResche 2006).

Evaluating Menstrual Cycle Changes in Pain Perception
In a meta-analysis performed by Riley et al. 1999, 16 studies were categorized by stimuli and assessed (Fillingim et al. 2009). For the cold pressor test, pressure, heat, and ischemic pain, sensitivity was lowest in the follicular phase, characterized by low hormone levels with estradiol increasing in the latter half. Electrical pain sensitivity, however, was lowest in the luteal and highest in the periovulatory phases. Only one of the included studies obtained hormonal measures. In a subsequent methodological review, researchers were skeptical of this analysis. They found inconsistent cyclical patterns in thermal, mechanical, and ischemic pain perception. The only notable pattern involved electrical pain with studies reporting decreased sensitivity in the early luteal phase (Sherman and LeResche 2006).

In a recent narrative review of cyclical pain response in healthy females, Martin 2009 analyzed the results of 19 human studies. To make findings comparable, the author redefined the reported cycle phases based on the actual test dates. Observed trends were summarized using three categories. The author noted that six studies reported no cyclical changes in pain sensitivity. However, five studies observed that pain sensitivity increased in phases characterized by fluctuating estradiol and increasing progesterone (late follicular and early luteal). Seven studies found that pain sensitivity increased in phases characterized by low or decreasing estradiol and progesterone (late luteal or early follicular). It should be noted that only four of the studies analyzed had blood progesterone and estradiol levels to verify menstrual cycle phase. An additional three studies confirmed ovulation through biological measures.

Hormonal Measures and Pain Perception
Hormonal assays are key to untangling the complex relationship between progesterone, estradiol, and pain. While countless studies have evaluated changes in pain perception over the menstrual cycle, only a small number have obtained either plasma or serum hormone levels. These measures allow for analysis of pain changes independent of experimental sessions or somewhat arbitrary divisions of the menstrual cycle (Sherman and LeResche 2006). Fillingim et al. 1997 conducted the first study that used blood-derived estrogen and progesterone levels to evaluate changes in pain sensitivity, specifically pain onset and threshold, over the menstrual cycle. A significant correlation was observed between elevated plasma estrogen levels and low thermal pain onset and threshold measures. In a study that examined diffuse noxious inhibitory control (DNIC), within the ovulatory phase, pain-induced analgesia was positively correlated with progesterone levels (Tousignant-LaFlamme and Marchand 2009). Ring et al. 2009 observed that within the luteal phase, progesterone, estradiol, and pain ratings from needle and catheter insertion were positively correlated. While Stening et al. 2007 used the cold pressor test to measure transition from mild to moderate pain (activation time) and noted that shorter activation times were significantly correlated with high progesterone levels; as were maximal pain ratings. Estradiol, however, was not significantly correlated with any of the results. Stening and colleagues (2007) also analyzed the combined impact of estradiol and progesterone on pain perception. When present together at high levels, estradiol and progesterone appeared to decrease pain sensitivity, with estradiol mediating progesterone’s apparent pronociceptive influence. Alternatively, several studies have not observed any correlations between hormone levels and pain measures (Craft 2007; Klatzkin et al. 2010; Kowalczyk et al. 2006).

Menstrual Cycle Disorders
Due to their close correlation with hormonal changes, several pain studies have evaluated females with cyclical medical conditions.
However, a major difficulty with this strategy is disentangling hormonal influences on pain perception per se from influences on the pathology causing the symptoms. Dysmenorrhea is a menstrual cycle condition characterized by extreme abdominal and back pain during menses. It has been speculated that low or decreasing progesterone levels may trigger dysmenorrheic symptoms (Martin 2009). In a clinical study, Granot et al. 2001 compared heat and laser pain thresholds in dysmenorrheic women and healthy females over four experimental sessions. Dysmenorrheic women were more sensitive to pain from both stimuli. For the laser stimuli, both groups appeared to have the lowest pain sensitivity in the luteal phase (high plasma progesterone and estradiol) and the highest during the follicular phase (increasing plasma estradiol). Cycle phase, however, did not affect dysmenorrheic women’s response to the heat stimuli. Similarly, Vincent and colleagues (2011) demonstrated increased sensitivity to noxious heat in dysmenorrheic women compared to pain-free controls, but found no influence of cycle phase in either group. In this study, the timing of the three experimental sessions was chosen to maximize endogenous variation in levels of estradiol and progesterone.

Premenstrual dysphoric disorder (PMDD) is a luteal phase condition characterized by extreme physical and emotional changes. While the underlying pathology of the condition remains unclear, it has been postulated that women with PMDD may have abnormal levels of sex steroid hormones and/or altered neurotransmitter regulation by these hormones. In support of this, two studies have shown luteal phase estradiol and progesterone levels to be higher in women with PMDD than controls (Straneva et al. 2002; Epperson et al. 2002). Interestingly, although there was no difference in cortical GABA levels between the groups, GABA levels decreased across the cycle in healthy women but increased in those with PMDD, with the steroid hormones appearing to exert opposing effects in the two groups (e.g., a positive correlation between GABA and both estradiol and progesterone in the women with PMDD and a negative correlation in the control women) (Epperson et al. 2002).

Chronic Pain Conditions and Hormonal Treatment

Given the prevalence of pain conditions in the female population, studies have focused on both evaluating differences in experimental pain response and deconstructing patterns of increased pain. Chronic pain conditions such as fibromyalgia, temporomandibular joint disorder (TMJD), and migraine appear to worsen at times of low or rapidly decreasing estradiol (LeResche et al. 2003), while symptoms from IBS, interstitial cystitis/painful bladder syndrome, and migraine as well as a variety of gynecological pain conditions can be improved by pharmacological manipulation of hormonal status (Mathias et al. 1994; Lentz et al. 2002; Silberstein and Goldberg 2007). Once again, effects of hormones on the underlying pathologies cannot be excluded; however, Sherman et al. 2005 did find that females with TMJD were more sensitive to experimental pain during the mid-luteal and menstrual phases.

Neuroimaging Studies

Neuroimaging technology has added an interesting dimension to the field (reviewed by Vincent and Tracey 2010). Studies of pain perception in healthy subjects suggest alterations in the cerebral response to noxious stimuli in differing hormonal states, although the findings from individual studies are not entirely consistent (Choi et al. 2006; de Leeuw et al. 2006). Unfortunately, to date, no studies have used neuroimaging techniques to investigate the relationship between steroid hormones and the cerebral response to pain in patients with a chronic pain condition. However, studies in healthy subjects further strengthen the evidence for interactions between sex hormones and endogenous pain modulatory systems; most strikingly for estradiol and the mu-opioid system.
(Smith et al. 2006), but also with GABA as discussed earlier and potentially other systems including the descending pain inhibitory system.

Summary

Conclusion

Despite the sheer number of studies, much work is needed to develop a cohesive understanding of individual and combined effects of estradiol and progesterone on pain perception. As noted by many reviews, reproducible, standardized methodologies are greatly needed (Martin 2009; Sherman and LeResche 2006; Riley et al. 1999).

The field of pain and hormones is complex, thus it is important to minimize as much research variation as possible.

References


### Femoral Nerve Block

**Definition**

Local anesthetic blockade of the femoral nerve that provides sensory innervation to the upper leg. It provides prompt analgesia and muscle relaxation in children with femoral shaft fractures.

**Cross-References**

► Acute Pain in Children, Postoperative

### Fentanyl

**Definition**

Fentanyl is a synthetic opioid that is a phenylpiperidine derivative and structurally related to meperidine.

**Cross-References**

► Postoperative Pain, Fentanyl

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**Fetal Pain During Prenatal Surgery**

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**Introduction**

The main argument in favor of fetal in utero analgesic treatment is that fetuses prematurely born are commonly entitled to receive routine analgesia, because newborns’ pain is a widely accepted fact. This is substantiated by observational studies, and by the anatomical development of the pain system, that is increasingly mature with age, in prematurely born fetuses. Thus, if a premature is entitled to analgesia, the same should be due to a fetus with the same level of development.

Conversely, those arguing against fetal analgesic treatment say that until a certain fetal age, the absence of a cortico-thalamic link is an absolute obstacle to awareness and to pain sensation. Moreover, they affirm that the fetus is in a continuous state of sleep, with almost absence of awareness that cannot be evoked neither by external stimuli, and therefore, it is in a continuous state of endogenous sedation.

Here, we will analyze three main data: (a) the development of pain pathways in the fetus; (b) fetus’ behavior; (c) fetal analgesia.

**Definition**

Fetal surgery has recently made rapid progresses (Wilson et al. 2010). Now it is possible to treat some mechanical anomalies before birth, and this in some cases has brought clear advantages to the babies, who have not to wait birth to be cured. For instance, fetal surgery is used in fetuses with congenital diaphragmatic hernia, in whom lung growth is triggered by percutaneous tracheal occlusion. It can also be used to treat urinary obstructions. Many fetal interventions remain investigational, but randomized trials have established the role of in utero
surgery for a number of conditions, making fetal surgery a clinical reality. The safety of fetal surgery is such that even nonlethal conditions, such as myelomeningocele repair, can be considered an indication. This leads to consider the opportunity of providing analgesia and anesthesia to the fetus. Of course, we have to wonder if a concern about fetal pain is justified, and this means to have an evidence-based opinion about the possibility for the fetus to feel pain.

**Characteristics**

**Development of Pain Pathways**

Anatomical and functional perception of pain develops throughout the gestational process. Peripheral receptors develop very early and may be seen by the ninth week of gestational age (GA) and are abundant by the 22nd week GA (Lowery et al. 2007). Four or five weeks after fertilization, pain receptors appear around the mouth, followed by nerve fibers, which carry stimuli to the brain. By 18 weeks GA, pain receptors have appeared throughout the body (Blackburn 2003). Connections between peripheral receptors and afferent fibers ending in the dorsal horn start as early as 8 weeks GA and the myelination of these fibers continues during development. Starting at 10–13 weeks GA, the afferent system located in the substantia gelatinosa of the spinal cord’s dorsal horn is developing. Connections to the thalamus begin at 14 weeks and are completed by 20 weeks GA, and thalamocortical connections or are present from 20 weeks GA, and are more developed by 26–30 weeks (Kostovic and Goldman-Rakic 1983). The neurons of the cerebral cortex begin a migration from the periventricular zone at 8 weeks gestation, and by 24–30 weeks GA, the cortex has acquired a full complement of neurons (Rodeck and Whittle 2008). Electroencephalographic activity appears for the first time at 20 weeks, becomes synchronized at 26 weeks GA, and reveals wake-sleep cycles at 30 weeks GA. It is possible to measure evoked potentials from the cortex from 24 weeks GA, with an objective evidence that a peripheral stimulus can cause cortical activation (Wilken and Gortner 2000).

An increase in stress hormones happens during fetal potentially painful transfusions: Piercing the fetal abdomen to access the intrahepatic vein (IHV) for transfusion is associated with substantial rises in these hormones from as early as 18 weeks GA. The median increase in beta-endorphin levels was 590 %, in cortisol levels was 183 %, and median increase in noradrenaline levels was 196 % (Giannakoulopoulos et al. 1994, Giannakoulopoulos et al. 1999).

It has been hypothesized that during surgery, despite general analgesia with opioids, metabolic changes due to pain might be present, indicating a production of stress hormones independent of consciousness, (Fitzgerald et al. 2003) but several studies show that analgesia inhibits both consciousness and the production of stress hormones (Desborough 2000), thus, this increase seems due to actual stress.

Clinical evidence for perception mediated by subcortical centers comes from infants and children with hydranencephaly (Marín-Padilla 1997; Takada et al. 1989). Despite total or near-total absence of the cortex, these children clearly possess discriminative awareness. They seem to distinguish familiar from unfamiliar people and environments and are capable of some social interaction, visual orienting, musical preferences, appropriate affective responses, and associative learning (Shewmon et al. 1999). Recent studies highlight the possibility of a subcortical form of consciousness, that has been recently evidenced by several authors in adult healthy patients (Denton et al. 2009; Merker 2007; Johnson 2005; Ohman et al. 2007).

**Fetal Behavioral States**

Fetuses spend most gestational time in sleep. Nevertheless term fetuses spend 9 % of their daytime in a wake state (Pillai and James 1990). Some argue that this continuous sleep state is induced by warmth and adenosine in the blood, but fetal adenosine levels (Yoneyama et al. 1996) are not distinct from mothers’ (Yoneyama et al. 2000), in whom it does not induce sleep or analgesia. Vibroacoustical stimulation, though little above the background noise, within the womb can induce awakening in fetuses (Leader and Fifer 1995). More conspicuous stimuli awaken
the fetus at birth. Fetal sleep can increase pain threshold, but cannot annihilate the possibility of experiencing pain.

**Fetal Analgesia**

In the case of major surgery, some researchers recommend to administer 20 microg/kg of intramuscular fentanyl to the fetus prior to the procedure, to increase the effect of volatile anesthetics that arrive to it through mother’s circulation (Schwarz and Galinkin 2003). Recent studies show that direct administration of 10 microg/kg fentanyl blunts the fetal stress response to intrauterine needling (Fisk et al. 2001). These authors showed that the magnitude of the beta-endorphin response to pain with these doses was halved, and the cerebral Doppler response was ablated. Comparison with control fetuses transfused without fentanyl indicated that the beta endorphin and cerebral Doppler response to intrahepatic vein transfusion with fentanyl approached that of nonstressful placental cord transfusions. Fentanyl significantly attenuated the endorphin and cerebrovascular response, but not the cortisol response (Fisk et al. 2001). This differential effect is not surprising. Using the same dose, intravenous fentanyl in preterm babies ablated most of the stress responses to surgery, but the reduction in the cortisol response after fentanyl failed to achieve statistical significance (Anand et al. 2001). It is worth highlighting that the amount of opioids that can arrive to the mother from the fetus is clearly low and relatively safe.

During open fetal surgery under maternal general anesthesia, inhalational agents given to the mother are still considered to provide adequate fetal anesthesia and produce uterine relaxation essential for successful surgery, so that additional analgesia for the fetus would be unnecessary. Nevertheless, several evidences against this approach should be considered: for instance after cesarean sections made with maternal general anesthesia, fetuses are born awake or are easily awakened at birth, providing evidence that maternal anesthetic drugs are not sufficiently anesthetic to the fetus.

Endoscopic procedures performed directly on the fetus, such as tracheal occlusion or meningocele repair, are usually performed under maternal local or regional anesthesia. As these procedures do not require maternal general anesthesia, additional fetal anesthesia is desired and is usually done by direct administration of opioids and muscle relaxants to the fetus. Two possible routes of administration for these drugs are injection into the umbilical cord and intramuscular injection into the fetus. Sometimes direct fetal administration of fentanyl and pancuronium is sometimes limited to cases where the fetus moves during the procedure in other cases, it is given routinely (Sutton 2008).

Some researchers utilized intra-amniotic opioids for fetal analgesia on lamb fetuses: They showed that greater plasma concentrations were obtained in the fetal lamb as compared with the ewe, suggesting that this route might be utilizable for humans.

The presence of an active cortical subplate (Anand et al. 2001) and of spino-thalamic connections seem sufficient to transmit the painful stimulus during the second half of pregnancy. Thus, the use of fetal analgesia is at least a due precautionary procedure.

**Summary**

In the second trimester of gestation, the incomplete development of the cortex does not yet consent awareness, but this does not seem to be an absolute obstacle to pain from the 20th week of GA. Evidence is present in adult patients for skills that do not need an involvement of the cortex. Several stimuli are processed without the need of the cortex (Mulckhuysen and Theeuwes 2010); nevertheless, these stimuli give useful visual information to the individual (Sewards and Seward 2000; Pasley et al. 2004), or provoke complex experiences such as fear (Ohman et al. 2007). A typical example of this is the perception of fearful stimuli or of unusual objects (for instance, during a mechanical skill like driving a car) that do not arrive to awareness, but that nevertheless can provoke complex reactions or behaviors: These stimuli do not arrive to awareness, but can affect consciousness. We can hypothesize a similar scenario for subcortical fetal processing of pain in this trimester: After the 20th week of GA, we should not exclude that pain can be felt by the fetus.
(Mahieu-Caputo et al. 2000), with possible long-term consequences (Lowery et al. 2007).

In the second half of pregnancy, fetuses have a higher pain threshold due to their sleep state, but this does not absolutely rule out pain. The presence of thalamocortical pathways and of the cortical subplate point out the possibilities of pain at this stage of development.

References


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**Fibroblast**

**Definition**

Fibroblast is a connective tissue cell.

**Cross-References**

▶ Wallerian Degeneration

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**Fibrocartilage**

**Definition**

Fibrocartilage is cartilage that is largely composed of fibers like those in ordinary connective tissue.

**Cross-References**

▶ Sacroiliac Joint Pain

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**Fibromyalgia**

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**Synonyms**

Chronic widespread pain; Fibrositis; Muscular rheumatism; Psychogenic rheumatism

**Definition**

Fibromyalgia is a condition characterized by chronic widespread pain, fatigue, unrefreshed sleep, and a tendency to experience generalized somatic symptoms.

**Characteristics**

Fibromyalgia is present in about 5% of the population. It is a syndrome of symptoms that include chronic widespread pain, fatigue, disordered sleep, and increased stress in association with abnormal neurosensory processing and nonspecific endocrine and autonomic dysfunction.

The original American College of Rheumatology (ACR) classification criteria for fibromyalgia included tenderness on pressure palpation at 11 or more of 18 specific tender points (Wolfe et al. 1990). Subsequently, the recognition that examination for tender points lacks validity and reliability has lead to the deletion of tender point examination from the diagnostic formulation for fibromyalgia.

Fibromyalgia is now a symptom-based diagnosis with the primary feature being widespread pain present for at least 3 months in association with other symptoms including fatigue, non-restorative sleep (NRS), and “somatic” symptoms such as anxiety, irritable bowel and bladder syndrome, cognitive inefficiency, tinnitus, and nausea. Justification for the shift from the physical examination criterion has been elicited by large studies that have developed diagnostic classification criteria scales. The ACR has now combined the widespread pain index (WPI) and the symptom severity (SS) scale to produce “simple, practical criteria for the clinical diagnosis of fibromyalgia” (Wolfe et al. 2010).

The Symptom Intensity Scale (SIS) is another scoring system for fibromyalgia (Wilke 2009). It combines the number of areas of pain present in the previous 7 days with a subjective measurement of fatigue as indicated on a 10-cm line to produce an overall...
SIS score, the level of which categorizes patients with possible fibromyalgia as having features “probably consistent with fibromyalgia” or “diagnostic.”

**Pathophysiology**

The pathophysiology of fibromyalgia is unknown and remains in dispute. Patients with fibromyalgia exhibit increased pain sensitivity to pressure, heat, cold, and electrical stimulation, but these features are not unique to fibromyalgia (Gracely et al. 2003).

Other markers of the disorder have been explored, but the results have not been consistent or reproducible. Nor are the abnormalities, when evident, expressed by all patients with fibromyalgia. Nor are they unique to these patients.

NRS, which is defined variably but includes the feeling of being unrefreshed upon awakening in spite of normal sleep duration, is common in the general population but more prevalent in FM and chronic fatigue syndrome (CFS) (Staud 2010). Fragmented sleep or difficulty getting to sleep is also common in FM patients. Although not unique to NRS, ▶ alpha(α)-delta(δ) sleep is more common in subjects with NRS than in healthy controls. The same anomaly occurs in other conditions and in 15% of healthy individuals (Carette 1995). Histological abnormalities have been reported in the muscles of patients with fibromyalgia, but no differences have been found in adequately controlled studies (Carette 1995). Nor have disturbances in muscle metabolism been verified (Carette 1995). Patients with fibromyalgia exhibit deficiencies in ▶ serotonin, increased levels of ▶ substance P in their cerebrospinal fluid, and abnormalities of the ▶ hypothalamic pituitary axis (Carette 1995), but these differences have not been shown to be unique to fibromyalgia.

One model that has been proposed is that fibromyalgia is due to an impairment of the diffuse noxious inhibitory control system (DNIC) (Gracely et al. 2003). The implication is that patients perceive spontaneous pain because of a lack of tonic inhibition of the central nociceptive pathways. The circumstantial evidence is that of conditioning, that painful stimuli produce analgesia in normal subjects but fail to do so in patients with fibromyalgia (Gracely et al. 2003).

Although this may be so, commentators have questioned whether the syndrome is due to altered central nociception or to hypervigilance, and if there is altered nociception, does it arise because of somatic factors or psychogenic influences (Cohen and Quintner 1998).

**Nosology**

The relegation of tenderness as a diagnostic criterion for diagnosis of fibromyalgia together with the development of symptom-based standards has provided clinicians with a more robust and reliable method for managing and studying patients with these symptoms. As a minimum, the diagnosis of fibromyalgia offers patients a diagnostic label that is more palatable than a diagnosis of widespread pain (Carette 1995).

**Treatment**

A variety of treatments have been applied to patients with fibromyalgia. Many treatments are based on hearsay or anecdote, and some of the conclusions from studies are based on previous diagnostic criteria for fibromyalgia. The EULAR report in 2008 found 146 studies eligible for review and made 9 recommendations for the management of fibromyalgia (Carville 2008). Exercise in general including heated pool exercise had some limited evidence and was included on the basis of expert opinion; tramadol had benefits over 13 weeks in a randomized controlled trial, but simple analgesics were supported and opioids refuted by expert opinion; antidepressants tended to reduce pain and improve function over a 12-week period but not over longer periods. A multidisciplinary approach to management was considered relevant, but this was again based on expert opinion rather than any evidence.

A meta-analysis of pregabalin found five high-quality trials (Straube 2010). Pregabalin seems to have similar efficacy to other medication treatments including duloxetine, combined paracetamol and tramadol, and amitriptyline 25 mg/day. Pregabalin enhances slow-wave sleep, and sodium oxybate (gamma-hydroxybutyrate)
reduces alpha EEG sleep, and both may have a role in symptomatic control of FM for those reasons (Staud 2010).

Cross-References

▶ Chronic Low Back Pain: Definitions and Diagnosis
▶ Fibromyalgia, Mechanisms, and Treatment
▶ Human Thalamic Response to Experimental Pain (Neuroimaging)
▶ Muscle Pain, Fibromyalgia Syndrome (Primary, Secondary)
▶ Myalgia
▶ Nocifensive Behaviors, Muscle and Joint
▶ Opioids and Muscle Pain
▶ Physical Exercise
▶ Psychological Aspects of Pain in Women

References


Fibromyalgia Syndrome

▶ Muscle Pain, Fibromyalgia Syndrome (Primary, Secondary)

Fibromyalgia, Mechanisms, and Treatment

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Introduction

Historically, fibromyalgia syndrome (FMS) was referred to as fibrositis, a term coined by Sir Edward Gowers at the turn of the century to describe the inflammation responsible for the stiffness and pain experienced by a group of non-arthritic patients. Fibromyalgia syndrome was the name adopted in 1990 by the American College of Rheumatology (Wolfe et al. 1990), and the consensus document on fibromyalgia at the MYOPAIN conference held in Copenhagen, Denmark, in 1992 provided the original description of the syndrome, the diagnostic criteria, and its prevalence. More recently, the American College of Rheumatology has provisionally approved a revised set of criteria for the diagnosis of fibromyalgia that does not require a tender point assessment (Wolfe et al. 2010).

Definition

Many chronic pain conditions display symptoms that overlap with those of FMS. Those conditions must be diagnosed separately and eliminated as the first step in the diagnostic protocol. The diagnostic criteria include widespread pain in all four quadrants of the body for a minimum of 3 months, originally based on tenderness to digital palpation at 11 of the 18 anatomically defined
tender points that are sensitive to pressure (mechanical pain). Wolfe et al. (2010) now recommend the diagnosis be based on the combination of a widespread pain index (WPI) and a symptom severity scale (SS) as follows: (WPI ≥ 7 and SS ≥ 5) or (WPI 3–6 and SS ≥ 9). Reductions in electrical and thermal pain thresholds have also been reported in patients with FMS, suggesting multimodal changes in pain sensitivity.

**Characteristics**

**Prevalence**
In North America, approximately 2% of the population, or greater than 3.7 million people, are estimated to suffer from FMS. The majority of these patients, approximately three out of four, are female. While it is the second most common syndrome presented in rheumatology clinics, the treatment is typically unsatisfactory, resulting in disability and handicap. Studies in several countries and ethnicities suggest a poor prognosis over several years of treatment.

**Comorbidity**
Chronic widespread pain is the primary complaint bringing most patients with FMS into the clinic. In addition to pain, non-restorative sleep, fatigue, anxiety and depression, interstitial cystitis, and irritable bowel syndrome are symptoms frequently diagnosed in patients with FMS. A higher incidence of cold intolerance, restless leg syndrome, cognitive dysfunction, rhinitis, and multiple chemical sensitivities is also more common in FMS patients than in healthy normal controls, adding to the perplexing mosaic of the disease. The etiology of FMS is unknown, and the relationships between pain and the other symptoms of FMS are unclear. Acute pain usually results in increased activation of the pituitary-adrenal and sympathomedullary pathways as well as growth hormone production. Patients with FMS, in contrast, present with hypofunction of the HPA, thyroidal, and gonadal axis; diminished growth hormone production (reviewed by Bennett 1998); and abnormally low sympathetic output (Clauw and Chrousos 1997). While exposure to stressful situations, including noise, lights, and weather, exacerbates symptoms of FMS, patients have an impaired ability to activate the hypothalamic-pituitary portion of the HPA axis as well as the sympathoadrenal system, leading to reduced adrenocorticotropic hormone (ACTH) and epinephrine responses. Yet many symptoms of FMS are sympathetically maintained, such as the neuropathic-type pain (reviewed by Martinez-Lavin 2007), abnormal heart rate variability, tilttable responses, and inappropriate responses to daily stressful situations.

**Unique Location of Tender Points**
While tender points are no longer necessary diagnostically, they offer insight into the etiology of pain. Tender points are generally distributed in areas whose primary afferent nerves project to spinal lumbar levels 3–5 and cervical levels 2–7 spinal cord segments. It may be of importance that these areas surround the thoracic 1 through lumbar 3 spinal cord segments that are involved with regulation of the sympathetic nervous system, whose function is significantly altered in patients with FMS. It is noteworthy that the pain of FMS is often in areas that receive a relatively low density of afferent innervation (trunk and proximal limbs) compared to areas normally considered “sensitive” by virtue of their dense innervation, e.g., the fingers, mouth, feet, and genitals. The sensitivity of these tender points does not, then, originate from a simple hyperactivity of all mechanically sensitive tissues but rather from an unknown, symmetrically distributed change in afferent input. Based on this and other psychophysical evidence of windup, the etiology of this syndrome is widely believed to include the CNS.

**Excitatory Amino Acids**
Excitatory amino acids, such as glutamate and aspartate, transmit pain signals, including those in patients with FMS. While the concentrations of most amino acids in the cerebrospinal fluid do not differ between subjects with FMS compared to healthy normal controls, a high degree of
correspondence was found between specific amino acids and the degree of pain reported at the 18 tender points (tender point index, TPI). Excitatory amino acid activity is known to trigger synthesis of nitric oxide (NO), a gaseous-signaling compound that is critical for the development and expression of chronic pain. Enhanced synthesis of NO results from a variety of depolarizing events, including excitatory amino acid and substance P activity, both of which lead to influx of calcium and activation of the enzyme NO synthase. NMDA activity is also associated with the production of nerve growth factor (NGF), a compound that regulates the synthesis of peptides in primary afferent C-fibers such as substance P.

**Substance P**
The first documentation of a biochemical characteristic consistent with chronic pain in patients with FMS was the increased concentration of substance P in their cerebrospinal fluid (Vaeroy et al. 1988; Russell et al. 1994; Welin et al. 1995), similar to that in many other pain states. Substance P is a neuroactive peptide released from small-diameter, unmyelinated primary afferent fibers, called nociceptors. Substance P is upregulated in chronic, inflammatory pain conditions by increased concentrations of NGF. Because substance P does not mediate acute pain but supports hyperalgesia, enhanced substance P content in the cerebrospinal fluid of patients with FMS is consistent with a chronic hyperalgesic state.

**Growth Factors**
Synthesis of nerve growth factor (NGF), a neurotrophin, in inflamed tissue is responsible for the upregulation of SP synthesis during chronic pain and the development of mechanical hyperalgesia and allodynia. Intravenous administration of NGF in humans causes muscle pain in a dose-dependent manner, primarily in bulbar and truncal musculature, and affects women more than men. While there is no gross inflammation at tender points to account for a peripheral source of NGF, delivery of NGF to the spinal area of mice or rats is sufficient to cause hyperalgesia. The concentration of NGF in the cerebrospinal fluid is normally low or unmeasurable in healthy individuals, but NGF is elevated in patients with primary but not secondary FMS (Giovengo et al. 1999). In addition, the concentration of brain-derived neurotrophic factor (BDNF), a mediator of pain in the peripheral nervous system, is elevated in the serum of patients with FMS (Laske et al. 2007). It is, therefore, possible that elevated concentrations of NGF and or BDNF are responsible for the hyperalgesia and allodynia associated with FMS, while secondary FMS results from conditions producing large areas of enhanced pain sensitivity.

**FMS and Thalamic Activity**
Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies in humans indicate that the thalamus as well as the anterior insula and S2 area are important in the perception of pain. Activation of the thalamus by pain normally initiates descending inhibitory activity that controls pain. Stimulation of the somatosensory thalamus has even been successfully used to treat extreme conditions of chronic pain in humans. Descending activity originating from the thalamus is sufficiently important that thalamotomy in rats results in both thermal as well as mechanical hyperalgesia. Although pain normally stimulates the thalamus in healthy individuals, a different pattern of activation occurs in patients with chronic pain. Regional blood flow in response to painful stimulation also differs in patients with FMS compared to that in normal control individuals (Risberg et al. 1995; Mountz et al. 1998; Petzke et al. 2000). These studies suggest that either the ascending spinothalamic nociceptive pathways are not fully functional or the thalamus responds abnormally to input from spinothalamic neurons. Because other parts of the CNS respond appropriately in patients with FMS, ascending activity appears sufficient. Rather, thalamic neurons likely fail to initiate sufficient descending inhibitory activity controlling nociceptive processing at the spinal cord level, a concept supported by altered nociceptive responses in patients with FMS (Staud et al. 2003).
Treatment
A variety of muscle relaxants, sedatives, analgesics, and drugs that promote sleep or combat fatigue are frequently used to treat symptoms of FMS. Unfortunately, even nonnarcotic analgesic drugs provide only temporary relief in most patients. When all else fails, narcotic analgesics are transiently effective in controlling flares, but not only does tolerance develop to their analgesic effect but long-term use can unmask an opioid-induced hyperalgesia. The efficacy and side effects of each compound vary greatly from one patient to another, but in general, their side effects are minimized and efficacy maximized by combination treatments using two drugs with distinct mechanisms of action. For example, gabapentin (Neurontin) is a compound used for neurogenic pain either alone or in combination with opioids. Gabapentin inhibits calcium channel activity, thereby minimizing the release of neurotransmitters.

Low doses of tricyclic antidepressants, such as amitriptyline, provide immediate but temporary analgesia, similar to their efficacy in other chronic pain conditions (O’Malley et al. 2000). The efficacy of this, and related drugs, is likely due to their action on nociceptive pathways and is not related to their antidepressant activity, which requires higher doses and longer periods of treatment to develop. Because tolerance to their analgesic activity develops, low doses (10 mg or less) are recommended in the beginning, gradually increasing by 10 mg as needed until the optimal dose of 70–80 mg is reached.

Only pregabalin (Lyrica), duloxetine (Cymbalta), and milnacipran (Savella) are FDA approved for the treatment of FMS symptoms. Duloxetine and milnacipran are antidepressants that inhibit serotonin and norepinephrine reuptake. Over the short term, this increases the synaptic concentration of these transmitters but, by doing so, influences their receptor sensitivity over the long term. In contrast, pregabalin binds to a voltage-dependent calcium channel in the central nervous system, reducing calcium influx into the nerve terminals and decreasing release of neurotransmitters such as glutamate, noradrenaline, and substance P. Pregabalin also increases the concentration of GABA, an inhibitory neurotransmitter, by increasing glutamic acid decarboxylase activity, the enzyme required for the synthesis of GABA.

Drug treatment to temporarily alleviate pain, including amitriptyline, NSAIDS, and even narcotic analgesics, should be geared to facilitate a new level of physical activity (reviewed by Clauw and Crofford 2003) as the most effective treatment for FMS is exercise (Sim and Adams 2002). Patients need to understand that exercise is the key to recovery, even if this means merely doubling their distance walked within the house from one day to the next. The exercise program should be initiated gradually, or it will temporarily exacerbate their symptoms. Heat therapy, in the form of a long hot bath immediately prior to bedtime, has been anecdotally reported to be effective for episodic bouts of intense pain. In contrast, cold exacerbates their condition and should be avoided.

Cross-References
▶ Chronic Low Back Pain: Definitions and Diagnosis
▶ Disability in Fibromyalgia Patients
▶ Fibromyalgia, Mechanisms, and Treatment
▶ Human Thalamic Response to Experimental Pain (Neuroimaging)
▶ Muscle Pain, Fibromyalgia Syndrome (Primary, Secondary)
▶ Myalgia
▶ Nocifensive Behaviors, Muscle and Joint
▶ Opioids and Muscle Pain
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▶ Psychological Aspects of Pain in Women

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**Fibrositis**

- **Fibromyalgia**
- **Myalgia**
- **Psychiatric Aspects of the Epidemiology of Pain**

**Fibrositis Syndrome**

- **Muscle Pain, Fibromyalgia Syndrome (Primary, Secondary)**
- **Myalgia**

**Field Block**

**Definition**

Local anesthetic injected through intact skin adjacent to the surgical site to create a subcutaneous wall encompassing the injury.

**Cross-References**

- **Acute Pain in Children, Postoperative**

**Fifth Lobe**

- **Insular Cortex, Neurophysiology, and Functional Imaging of Nociceptive Processing**
Firing of Suburothelial Afferent Nerves

Definition

Firing of suburothelial afferent nerves and the threshold for bladder activation may be modified by both inhibitory (e.g., NO) and stimulatory (e.g., ATP, tachykinins, prostanoids) mediators. These mechanisms can be involved in the generation of detrusor overactivity causing urgency, frequency, and incontinence, but also bladder pain.

Cross-References

► Opioids and Bladder Pain/Function

First and Second Pain

Definition

When a needle is pierced into the skin of an extremity, the subject feels typically an immediate stinging pain followed after a short delay by a second wave of predominantly burning pain. These two pain phenomena are called “first” and “second” pain. They are attributed to the excitation of A-delta and C-fibers. Since the former have conduction velocities up to 30 m/s, the nerve impulses reach the central nervous system so quickly that no delay is experienced. C-fibers having conduction velocities around 1 m/s convey their impulses considerably slower. If the needle prick is applied to the foot of a grown-up person, the delay could be more than a second. If the sting is applied to the face, the two pains are not separated by a delay due to the short conductance distance.

Cross-References

► Encoding of Noxious Information in the Spinal Cord
► Opioids, Effects of Systemic Morphine on Evoked Pain

First and Second Pain Assessment (First Pain, Pricking Pain, Pin-Prick Pain, Second Pain, Burning Pain)

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Synonyms

Burning pain; First pain assessment; Pin-prick pain; Pricking pain; Second pain assessment

Definition

Prior to the development of methods for physiological and anatomical characterization of axons within peripheral nerves, Henry Head concluded that the skin was served by epicritic and protopathic afferent systems in which each gave rise to its own particular qualities of sensations (Head 1920). Epicritic pain, for example, was said to be accurately localized, to not outlast the stimulus, and to provide precise qualitative information about the nature of the stimulus. Thus, epicritic pain could be elicited by mild pricking of the skin with a needle, a form of pain known to almost everyone as pricking pain. In contrast, protopathic pain was described as less well localized, slow in onset, often outlasting the stimulus, and summing with repeated stimulus application. Protopathic pain was considered more difficult to endure and contained special feelings of unpleasantness or “feeling tone.” The concept of “protopathic” has been applied to burning pain, aching pain, throbbing pain, and dull pain. Head based these ideas largely on observations made of his own experiences of pain, after nerve division and during nerve regeneration.

With the advent of modern electrophysiological and neuroanatomical techniques, it became clear that pain depended on two types of peripheral nerve axons. The first is that of thinly myelinated A-delta axons, whose conduction
velocities range between 3 and 30 m/s, and the second is that of unmyelinated C axons, whose conduction velocities range between 0.5 and 2.0 m/s. Based on their differences in conduction velocity and reminiscent of the functional dichotomy proposed by Head, Zotterman proposed that A-delta and C afferent axons could account for first and second pain, which often occur in response to a brief intense stimulus to the hand or foot (Zotterman 1933). Landau and Bishop explicitly related first pain to epicritic pain and second pain to protopathic pain (Landau and Bishop 1953). Interestingly, they based their conclusions as a result of an approach similar to that of Head. They carefully observed and recorded their own pain experiences in response to “experimental” pain stimuli, before and after selective conduction block of A-delta or C axons of peripheral nerves. They used local injections of dilute solutions of procaine to selectively block C axons within small nerve branches in order to study pain from impulses in A-delta axons. They selectively blocked all myelinated axons in peripheral nerves of their lower arms by means of a 250 mmHg pressure cuff in order to assess the types of pains evoked by impulses in C axons. They applied various types of painful stimuli to skin, fascia, and periosteal surfaces, including bee stings, turpentine injections, intramuscular KCL injections, and application of deep and sharp pressure with mechanical probes. When they blocked C axons with procaine, well-localized brief-duration stinging sharp pains, such as those elicited by pinpricks (i.e., pricking pain or first pain), were preserved, but prolonged, deep, and diffuse burning pains evoked by inflammatory stimuli, such as the second pain from a bee sting, could no longer be elicited. When they blocked all myelinated (A) axons by means of the blood pressure cuff, the latter types of pain could be elicited and were more intense than before blockade of myelinated axons.

These general observations have since been corroborated in conventional studies, wherein investigators studied responses of volunteer participants (Price 1972, 1999; Collins et al. 1960). An important aspect of the study by Collins et al. was that compound action potentials were monitored (Collins et al. 1960). They placed stimulating and recording electrodes under the sural nerve of cancer patients undergoing anterolateral chordotomy for relief of pain. They found that stimulation of A-delta axons produced sharp pricking pain sensations that were accurately localized. When A-delta axons were blocked by cold, stimulation of C axons at a rate of 3/s resulted in summating unbearable diffuse burning pain that was not as well localized.

The association of first and second pain with impulses in A-delta and C axons and the relationship of these two types of pain to epicritic and protopathic pain have pivotal roles in the history of pain research. However, like all functional dichotomies, it is important not to overgeneralize their explanatory role, for example, to prematurely label different central pain-related pathways as “epicritic” or “protopathic.” Even Head warned against this type of error, when he concluded that epicritic and protopathic systems recombined once they entered the dorsal horn (Head 1920). Thus, although zones of relatively pure epicritic or protopathic sensibility could be found after dorsal root or peripheral nerve lesions, he noted that such zones were never observed after lesions of the spinal cord or brain. More than 40 years before electrophysiological studies were carried out on dorsal horn nociceptive neurons, Head anticipated the synaptic convergence of two functional types of primary nociceptive afferents (known since as A-delta and C) onto neurons of the dorsal horn.

One must also take note of the fact that A-delta and C nociceptive afferents are rarely activated in isolation. Most acute pains are likely to reflect a combination of input from A-delta and C nociceptive afferents and, in most cases, from non-nociceptive afferents as well. Indeed, the composition of input from different types of nociceptive and non-nociceptive afferents undoubtedly contributes a lot to the diverse qualities of both painful and non-painful somatic sensation (Price 1999). However, many long-duration pains, especially those that are diffuse, spatially spreading, and especially unpleasant in their “feeling tone” may depend to a greater extent
on tonic input from C nociceptive afferents than from input from A-delta nociceptive afferents. The initial pains from abrupt injuries (e.g., stepping on a tack) are likely to depend heavily on A-delta nociceptive afferents.

**Characteristics**

**Temporal Characteristics of First and Second Pain and Their Relationships to Neural Mechanisms**

First and second pains are often easily distinguished when a sudden tissue damaging or potentially tissue-damaging stimulus occurs on a distal part of the body, such as the hand or foot (Fig. 1).

The 0.5–1.5-s delay between the two pains occurs as a result of the fact that nerve impulses in C axons travel much slower (0.5–1.5 m/s) than those in thinly myelinated A axons (6–30 m/s). Lewis and Pochin independently mapped the body regions wherein they experienced both first and second pains (Lewis and Pochin 1938). The body maps of both Lewis and Pochin were nearly identical. The maps showed that first and second pain could be perceived near the elbow but not the lower trunk, even though both sites were about the same distance from the brain. The reason for this difference is that C fibers that supply the trunk have a short conduction distance to the spinal cord, whereas C fibers that supply the skin near the elbow have a long conduction distance. Once both “trunk” and “elbow” C fibers reach the spinal cord, they synapse on nerve cells that have fast-conducting axons. As a result of differences in peripheral conduction distance and time, first and second pain can be discriminated at the elbow but not the trunk.

Later, studies using psychophysical methods replicated and extended the ones just described (Price 1972, 1999). These methods relied on delivering brief and well-controlled experimental stimuli to the distal part of an extremity, such as the hand or foot. These regions were chosen because they allowed for discrimination of first and second pain related to impulse conduction in A-delta and C axons, respectively. Reaction time
measurements were used to confirm that subjects could indeed distinguish the two pains. Both trained and untrained subjects reported qualities of first pain as “pricking,” “stinging,” or “sharp” (i.e., pin-prick pain), without provocation or suggestion that such qualities existed. Subjects were trained to judge the perceived magnitudes of first and second pain by squeezing a handgrip dynamometer in some experiments (Price et al. 1977) or using a mechanical visual analogue scale in others (Price et al. 1994). Mean psychophysical ratings of intensities of first pain during trains of computer-driven heat pulses (2.5 s duration, peak temperature 52°C) decreased progressively (Price 1999; Price et al. 1977, 1994) and stayed the same in the case of 5–9 mA electric shocks (Price 1972; Price et al. 1994). Unlike first pain, second pain progressively increased in mean intensity and duration throughout a series of shocks or heat pulses, when the interstimulus interval was less than 3 s but not when it was 5 s (Price 1972, 1999; Price et al. 1977, 1994) (Fig. 2). Moreover, second pain became stronger, more diffuse, and more unpleasant with repeated heat pulses or repeated electrical shocks.

When the same types of heat pulses or electrical shocks described above are applied to the skin of monkeys, spinothalamic tract neurons within the spinal cord dorsal horn respond with a double response (i.e., two sets of impulse discharges) (Price 1999), as shown in Fig. 1. The earlier of the two is related to synaptic input from A-nociceptors,
and the delayed response is related to synaptic input from C nociceptors (Price 1999; Price et al. 1977). Similar to first pain, the first response decreases or remains the same during heat pulses or shocks, respectively, whereas the second delayed response to heat pulses or shocks increases progressively both in magnitude and duration. Similar to second pain, temporal summation of the delayed neural response was observed when the interstimulus interval was 3 s or less but not 5 s (Price 1999). For neurons, this temporal summation has been termed “windup” (Price 1999). Moreover, this summation must occur within the spinal cord dorsal horn because similar experiments conducted on peripheral A and C nociceptors show that their responses do not increase with stimulus repetition (Price et al. 1977, 1994). Thus, temporal summation of second pain depends on mechanisms of the central nervous system (i.e., dorsal horn neurons), not changes in peripheral receptors.

These psychophysical-neural parallels have been confirmed not only in the case of single neurons of the spinal cord dorsal horn but also in the case of neural imaging at the level of the somatosensory region of the cerebral cortex (Tommerdahl et al. 1996). Using a brain imaging method of intrinsic optical density measurements (OIS), Tommerdahl and colleagues (Tommerdahl et al. 1996) imaged neural activity within the primary somatosensory cortex of anesthetized squirrel monkeys as their hands were repetitively tapped with a heated thermode. These taps reliably evoke first and second pain in human subjects. Their method of neural imaging has a high degree of both spatial and temporal resolution, measuring local cortical neural activity within 50–100 µm and sampling neural activity that has occurred within a third of a second. Heat taps produced localized activity in two regions of the primary somatosensory cortex, termed 3a and 1. When a train of heat taps was presented at a rate of once per 3 s, each tap evoked delayed neural activity within these regions. The neural response to each tap grew progressively more intense and larger in area with each successive tap. This temporal summation of this neural response paralleled human psychophysical experiences of second pain in several distinct ways. Both types of responses summate at the same rate of stimulus repetition and have a similar growth in intensity during a series of heat taps. The perceived skin area in which second pain is perceived and the area of cortical neural activity both increase with repeated heat taps.

Windup and temporal summation of second pain are related to synaptic interactions between C-nociceptive afferents and dorsal horn neurons. These interactions involve long-duration excitatory processes related to the release of neurotransmitters such as glutamate/aspartate and neuromodulators such as substance P. These agents respectively activate NMDA (N-methyl-D-aspartate) receptors and neurokinin 1 receptors, leading to prolonged depolarizations (Thompson and Woolf 1990, for review). Thus, NMDA receptor antagonists block both temporal summation of second pain and the “windup” responses of dorsal horn neurons to repeated C fiber input (Price 1999). Windup is related to hyperalgesic states that can be produced experimentally as well as those occurring in pathophysiological pain, such as postherpetic neuralgia (Arendt-Nielsen 1997; Dubner 1991). Indeed, slow temporal summation has long been considered a central neural mechanism that has a role in pathophysiological pain (Noordenbos 1959).

References


First Pain

Definition

First pain is a rapid onset, sharp, pricking noxious sensation that is associated with the activation of Aδ nociceptors. When a noxious stimulus is sufficient to activate both Aδ and C nociceptors, first pain is perceived before second pain due to differences in nerve conduction velocity.

Cross-References

- Encoding of Noxious Information in the Spinal Cord
- First and Second Pain Assessment (First Pain, Pricking Pain, Pin-Prick Pain, Second Pain, Burning Pain)
- Opioids, Effects of Systemic Morphine on Evoked Pain
Fitness Training

▶ Physical Exercise

Fits of Pain

▶ Pain Paroxysms

Flare

▶ Nociceptor, Axonal Branching

Flare, Flare Response

Definition

See also “neurogenic inflammation” and “axon reflex.” Since the flare response is dependent on the extension of the terminal arborization of the C-fibers mediating this axon reflex response, i.e., their receptive fields, flare sizes vary in different species and depend also on the type of nerve fibers involved. Rodents do not show a visible flare response since the receptive fields of their C-afferents are small. They produce, however, a neurogenic plasma extravasation upon the stimulation of C-fibers. In humans, the flare responses following histamine stimulation are particularly large due to the large receptive fields of the histamine-sensitive C-fibers.

Cross-References

▶ Nociceptor, Axonal Branching
▶ Polymodal Nociceptors, Heat Transduction
▶ Quantitative Thermal Sensory Testing of Inflamed Skin

Flexion Exercise

▶ Exercise

Flexion Withdrawal Reflex

Definition

This is a protective reflex usually elicited in the lower limb and was originally described by Charles Sherrington as “the withdrawal of a limb from an offending stimulus.” As originally characterized, it involved the activation of flexor muscles via a group of afferent nerve fibers called “flexor reflex afferents” with corresponding inhibition of extensor muscles. However, more recent research has revealed that the flexion withdrawal reflex has a more complex modular organization, its activation being contingent upon the area of skin being stimulated. Nevertheless, in the adult, the nociceptive (i.e., produced by noxious stimuli) flexion withdrawal reflex has proved invaluable as a model of nociceptive processing, and shows a clear correlation with pain perception in terms of threshold, peak intensity, and sensitivity to analgesics. However, in the newborn infant, the flexion withdrawal reflex can also be evoked with low-intensity mechanical stimuli to the foot, such as calibrated monofilaments (also called von Frey hairs), and has a much lower threshold than the nociceptive flexion withdrawal reflex in the adult.

Cross-References

▶ Infant Pain Mechanisms

Flinching

Definition

At its most vigorous, flinching of the paw and/or hindquarters is paw shaking, and when less
vigorously, rapid paw lifting. It is usually seen as drawing the paw under the body and rapidly vibrating it, and this causes a shudder or rippling motion across the back which is easy to observe even when the paw is not visible. Each episode is recorded as a single flinch.

Cross-References

▶ Formalin Test

Flip-Flop Isoform of AMPA Receptors

Definition

AMPA receptors have four subunits named GluR1-4 (or GluRA-D), respectively. Each subunit of the AMPA receptor exists in two isoforms, so-called flip and flop due to alternative splicing of a 115-base pair region encoding 38 amino acid residues immediately preceding the predicted fourth membrane domain. The flip and flop isoforms of AMPA receptors may be differentially involved in pain transmission and response to injury.

Cross-References

▶ Descending Circuitry, Molecular Mechanisms of Activity-Dependent Plasticity

Flunarizine

Definition

Calcium channel, dopamine, and histamine antagonist used in the preventive treatment of migraine.

Cross-References

▶ Headache Due to Arteritis

Fluorocitrate

Definition

Fluorocitrate blocks the activation of glial cells, without directly affecting neurons, and functions to inhibit the activity of aconitase, an enzyme in the Krebs cycle of glia, but not neurons. Peri-spinal administration of fluorocitrate blocks exaggerated pain.

Cross-References

▶ Cord Glial Activation

Flurbiprofen

Definition

Flurbiprofen is a nonsteroid anti-inflammatory drug (NSAID), which inhibits the formation of prostaglandins by cyclooxygenase. It is selective for COX-1, thus inhibits COX-1 at lower concentrations than COX-2.

Cross-References

▶ Cyclooxygenases in Biology and Disease

fMRI

▶ Functional Magnetic Resonance Imaging

fMRI Imaging and PET in Parietal Cortex

▶ PET and fMRI Imaging in Parietal Cortex (SI, SII, Inferior Parietal Cortex BA40)
Focal Pain
Definition
Focal pain is that which is experienced at one site, superficial to the underlying nociceptive lesion.

Cross-References
▶ Cancer Pain, Goals of a Comprehensive Assessment

Focused Analgesia
Definition
Focused analgesia is based on increased and directed attention to that part of the body for which suggestions of analgesia have been given. For example, suggestions for numbness in the hand may produce the experience of numbness as well as reduced pain sensation.

Cross-References
▶ Hypnotic Analgesia

Follicular Phase
Definition
The follicular phase is the time during which a single dominant ovarian follicle develops. The follicle should be mature at mid-cycle for ovulation. The average length of this phase is about 10–14 days. Variability in the length of this phase is responsible for variations in total cycle length.

Cross-References
▶ Premenstrual Syndrome

Forced-Choice Procedure
Definition
Forced-choice procedure is a statistical decision theory method in which a sensory decision is made after two or more stimulus presentations.

Forearm Ischemia Procedure
Definition
▶ Tourniquet Test

Forearm Occlusion Pain
Definition
▶ Tourniquet Test

Forebrain
Definition
Forebrain is the part of the brain including the cerebral cortex, limbic system, and hypothalamus.

Cross-References
▶ Forebrain Modulation of the Periaqueductal Gray and Its Role in Pain
Forebrain Modulation of the Periaqueductal Gray and Its Role in Pain

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Introduction

Forebrain Inputs to PAG
In the 1980s and 1990s, tract-tracing studies from a number of laboratories (e.g., Beitz 1982; Shipley et al. 1991) revealed an important feature of the PAG; afferent inputs to the PAG arise from a staggering number of cortical and subcortical forebrain sites. These inputs to the PAG are much heavier than previously suspected and terminate with a remarkable degree of topographic specificity. Major identified forebrain afferents to the PAG include the medial prefrontal cortex (MPF), the medial preoptic area (MPO), the central and medial nuclei of the amygdala (CeA, MeA), the ventromedial hypothalamus (VMH), and the paraventricular nucleus of the hypothalamus (PVN).

Definition

The midbrain ➤ periaqueductal gray (PAG) and its descending projections to the ➤ rostral ventromedial medulla (RVM) comprise a critical descending neuroanatomical pathway modulating pain and analgesia. The PAG projects heavily and directly to the RVM, which in turn projects to the ➤ dorsal horn of the spinal cord. Both pain and analgesia are modulated by emotional, motivational, and cognitive factors indicating higher-order cortical and subcortical ➤ forebrain modulation of the PAG-RVM-spinal cord pathway. Anatomical studies have demonstrated that the PAG predominantly receives afferents from the forebrain, including cortical and subcortical sites involved in nociception. These forebrain projections terminate with a high degree of topographical specificity within the PAG, forming longitudinal input columns extending throughout the rostrocaudal extent of the PAG and activating output neurons projecting to the RVM. Major identified forebrain afferents to the PAG include the medial prefrontal cortex (MPF), the medial preoptic area (MPO), the central and medial nuclei of the ➤ amygdala (CeA, MeA), the ventromedial ➤ hypothalamus (VMH), and the paraventricular nucleus of the hypothalamus (PVN).

Characteristics

Medial Prefrontal Cortex (MPF)
The PAG receives dense inputs from large groups of neurons in the orbital, medial prefrontal, and lateral (insular and perirhinal) cortices (Beitz 1982; Shipley et al. 1991; Floyd et al. 2000). In total, inputs to the PAG arise from at least 8 distinct cytoarchitectonic fields in the medial prefrontal and lateral cortices (Shipley et al. 1991). ➤ Retrograde tracing demonstrates that projections to the PAG from the cerebral cortex arise from all fields of the medial prefrontal cortex infralimbic, prelimbic, anterior cingulate, and precentral medialis. Equally extensive projections arise from the lateral suprarhinal (insular cortex) and perirhinal cortical areas. Anterograde tracing reveals that the pattern of terminal labeling from each medial or lateral cortical field is highly organized and selectively targets discrete, columnar subregions of the PAG along its entire rostrocaudal axis. Inputs from different cortical fields terminate as different, largely complementary, longitudinal columns. Imaging studies in humans have shown that anterior cingulate and insular orbital cortices are consistently activated by the sensory-perceptual and affective (i.e., emotional or unpleasant) aspects of pain (Price 2000; Rolls et al. 2003). Analgesia, including opiate receptor-dependent analgesia, can be elicited from the anterior cingulate and insular cortices (see
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Fig. 1 Photomicrograph illustrating projection neurons in the CeA of the female rat as identified by retrograde tracing from the lateral/ventrolateral PAG and observed as a brown precipitate following immunohistochemical processing. Also shown is Fos expression to identify neural activity in CeA neurons and CeA-PAG projection neurons, observed as a black precipitate, following 24 h of hindpaw inflammation.

Shipley et al. 1991; Burkey et al. 1996), and both areas are activated in humans following opioid or placebo treatment (Petrovic et al. 2002).

Central and Medial Nuclei of the Amygdala (CeA, MeA)

Projections from the amygdala to the PAG arise predominantly from the central and medial nuclei of the CeA. The CeA projects in a columnar manner to the PAG (Shipley et al. 1991). Additionally, a substantial population of PAG neurons project to the CeA. The CeA projection terminates as rostrocaudally oriented input columns that focally target different PAG subdivisions. The dorsomedial and lateral/ventrolateral subdivisions are especially heavily targeted (Shipley et al. 1991). Retrograde tract-tracing from the lateral/ventrolateral PAG reveals a dense population of projection neurons in the CeA of both male and female rats, and these projection neurons are activated by 24 h of hindpaw inflammation, observed as colocalization with Fos as a measure of neural activity (Fig. 1). There is also a dense projection of neurons from the MeA to the lateral/ventrolateral PAG that are also active during inflammatory pain (Fig. 2). The CeA is a key component of circuits involved in defense reactions, as well as the mediation of both conditioned and innate fear-related responses. In this regard, it is noteworthy that conditioned and unconditioned fear and aversive responses are accompanied by antinociception (Helmstetter and Tershner 1994). Stimulation of the CeA produces analgesia (Shipley et al. 1991; Oliveira and Prado 2001), and the CeA is involved in analgesia elicited by systemically administered opiates (Manning and Mayer 1995). It is reasonable to speculate, therefore, that CeA projections to the PAG may mediate antinociceptive responses that accompany fear and aversive responses. In agreement with this hypothesis, lesions of the PAG and RVM attenuate analgesia associated with aversive conditioned responses (Helmstetter and Tershner 1994), and PAG lesions block CeA-stimulation-produced analgesia (Oliveira and Prado 2001).

Medial Preoptic Area (MPO)

The MPO-PAG projection is very dense and exhibits columnar organization, similar to the CeA-PAG projection. This projection arises from neurons in several cytoarchitectonically distinct subdivisions of the MPO, including the sexually dimorphic medial preoptic nucleus (Fig. 3). These neurons are also activated following 24 h of inflammation in the rat hindpaw.
Injections of anterograde tracers into the MPO label dense, highly organized, and topographically specific projections to the PAG. A hallmark of this projection, like other forebrain inputs studied to date, is that it forms longitudinally organized input columns that selectively target discrete subregions of the PAG (i.e., the dorsomedial and lateral/ventrolateral PAG) along its rostrocaudal axis. In particular, MPO inputs to the PAG selectively terminate within the lateral/ventrolateral caudal PAG, where output neurons to the RVM are selectively located (Murphy and Hoffman 2001). Activation of the MPO by a variety of physiological factors also activates longitudinally organized columns of PAG neurons, including those that project to the
ventral medulla (Murphy and Hoffman 2001; Normandin and Murphy 2008). The MPO is sexually dimorphic and plays a key role in neuroendocrine and steroidal regulation and maternal/reproductive behaviors. Nociceptive thresholds shift across the estrus cycle, with steroid hormone administration and during reproductive activities (see ▶ Sex Differences in Descending Pain Modulatory Pathways). Both the MPO and the PAG contain high levels of estrogen and androgen receptors (Murphy and Hoffman 2001; Loyd and Murphy 2008). The MPO-PAG projection neurons also coexpress the estrogen receptor ERα (Fig. 4). In this regard, it is interesting to note that there are sex differences in pain thresholds as well as sex differences in how inflammatory pain activates the PAG-RVM circuit (Loyd and Murphy 2006). Furthermore, the PAG-RVM pathway is anatomically and functionally sexually dimorphic (Loyd and Murphy 2006) and is essential for the observed sexual dimorphism in morphine analgesia (Loyd et al. 2008). The MPO, therefore, may provide a key link mediating hormonal influences on nociceptive thresholds and may also regulate descending nociception during maternal/reproductive behaviors (Murphy et al. 1999). Consistent with this hypothesis, stimulation of the MPO activates PAG neurons that project to the RVM (Rizvi et al. 1996), inhibits dorsal horn spinal cord neuronal responses to nociceptive stimuli, and also elicits analgesia (see Shipley et al. 1991; Zhang and Ennis 2005).

Hypothalamic Projections to the PAG
There is also evidence of various hypothalamic nuclei projections to the lateral/ventrolateral PAG as observed by retrograde tract-tracing, including the ventromedial hypothalamus (VMH; Fig. 5) and the paraventricular nucleus of the hypothalamus (PVN; Fig. 6). These hypothalamic nuclei are known to modulate fear and stress responses, as well as sex and satiety behaviors. Hypothalamic projections to the PAG likely play a role in modulating these behavioral responses during pain and analgesia; however, little research has addressed these possibilities. Future research is warranted based on known anatomical connectivity between the hypothalamus and the descending pain inhibitory system.

PAG-Forebrain Afferents Coordinate a Multitude of Behavioral Responses
There has been a growing recognition that the PAG itself is far more complex than initially suspected and is clearly involved in many more physiological functions than nociception. For example, stimulation of different columnarly organized regions of the PAG produces...
a number of distinctly different behavioral and physiological responses including vocalization, autonomic changes, sexual/reproductive behaviors, and fear and rage reactions (for review see Shipley et al. 1991; Murphy et al. 1994; Murphy and Hoffman 2001; Loyd and Murphy 2009, Loyd and Murphy 2008). Not surprisingly, many of the forebrain sites that project to the PAG are also known to regulate similar functions. Based on these findings, a more integrative conceptual framework has been adopted guided by the working hypothesis that the PAG is a structure that plays a central role in the production of certain stereotypical behaviors (e.g., reproduction, defense reactions, vocalization) essential to the animal’s survival (Loyd and Murphy 2009). These behaviors require rapid, profound autonomic adjustments and simultaneously, significant alterations in pain thresholds. From this perspective, it is reasonable to consider that more highly elaborated forebrain structures interact with the PAG to coordinate

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Fig. 5 Photomicrograph illustrating VMH-PAG projection neurons in the female rat identified by retrograde tract-tracing from the lateral/ventrolateral PAG and observed as brown precipitate following immunohistochemistry. Also shown are Fos-positive VMH neurons and VMH-PAG output neurons indicating neural activity following 24 h of hindpaw inflammation

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Fig. 6 Photomicrograph illustrating PVN-PAG projection neurons in the female rat identified by retrograde tract-tracing from the lateral/ventrolateral PAG and observed as brown precipitate following immunohistochemistry. Also shown are Fos-positive PVN neurons and PVN-PAG output neurons indicating neural activity following 24 h of hindpaw inflammation
antinociceptive, behavioral, and autonomic responses in concert with the dominant role of the forebrain in cognitive and emotional processing. Descending PAG output neurons also exhibit columnar organization, such that different output columns terminate with medial to lateral specificity in the ventral medulla in sites involved in nociception, autonomic responses, sexual/reproductive behaviors, and vocalization (Murphy and Hoffman 2001; Murphy et al. 1999; Loyd and Murphy 2008, Loyd and Murphy 2009, Loyd and Murphy 2006). Taken together, these findings suggest that forebrain sites may trigger or modulate specific nociceptive and autonomic adjustments via activation of discrete columns of PAG output neurons.

**Summary**

The PAG and the RVM are major nodes for bidirectional modulation of nociception and spinal cord neuronal responses to noxious sensory input. The PAG-RVM circuit is demonstrably central to analgesia elicited by activation of endogenous opioidergic systems as well as that resulting from exogenously administered opioids. Nociceptive regulation is but one aspect of this circuit as the PAG is clearly a highly organized structure that integrates defensive, fear/anxiety, and hormonal/reproductive behaviors in discrete columns that extend longitudinally through the structure. These columns receive dense and topographically specific input from cortical and subcortical forebrain areas centrally involved in these same functions. Some forebrain areas also project in parallel to the RVM, and the functional significance of such dual projections is not known. In humans, whose behavior is dominated by the massive and highly elaborated forebrain, the projections to the PAG and RVM are likely to regulate nociception in concert with forebrain-mediated cognitive and emotional processing of pain and its perceived impact.

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**References**


**Formalin Test**

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**Synonyms**

Nociception induced by injection of dilute formaldehyde

**Definition**

The formalin test refers to the quantification of characteristic nociceptive behaviors that occur in response to subcutaneous (s.c.) or intradermal injection of a dilute solution of formaldehyde in 0.9 % saline, typically into the dorsal or plantar hindpaw of rodents.

**Characteristics**

The formalin test was originally described by Dubuisson and Dennis (1977) using 50 µl of 5 % formalin injected s.c. into the dorsal surface of one forepaw in rats and cats. “Five percent formalin” consisted of 1 ml of saturated formaldehyde (37 %) in water + 19 ml 0.9 % saline (i.e., 1.85 % formaldehyde). It is now more common to inject between 0.2 % and 5 % formalin into the dorsal or plantar hindpaw, using 20–50 µl in rats or 10–25 µl in mice. Another common site is the lateral aspect of the muzzle, or the temporomandibular joint, in rats, as a model of orofacial pain (Clavelou et al. 1995). The hindpaw has replaced the forepaw as a preferred site, because rats and mice frequently lick the forepaw in normal grooming. The formalin test has also been used in other species, including guinea pigs, rabbits, primates, crocodiles, domestic fowl, and octodon degus (Tjølsen et al. 1992).

Nociceptive behaviors increase with formalin concentration in rats and mice but reach a plateau between 2 % and 5 % formalin regardless of the scoring method used (see below) (Tjølsen et al. 1992; Coderre et al. 1993; Abbott et al. 1995; Sawynok and Liu 2003). With further increases in concentration, the magnitude and duration of the behavioral response are not increased; rather the animal’s behavior becomes more disorganized, and the nociceptive scores may actually fall. Formalin concentrations of 1 % or less are useful for detecting the actions of weak analgesics, avoiding ceiling effects (Abbott et al. 1995; Sawynok and Liu 2003).

Factors that influence the magnitude of the response include the site of injection (plantar injections produce greater responses), age of the
animal (responses are greater in infant rats), the strain, the degree to which the animal is habituated to handling, and the testing environment (unfamiliar environments can produce stress-induced analgesia), level of morbidity (e.g., time since surgery), and temperature of the animal colony and the testing environment (heat increases peripheral blood flow and the inflammatory response). Other environmental factors, such as sounds, odors, light, atmospheric pressure, or even activity of humans in the test room, can also influence the expression of nociceptive behaviors. Formalin concentrations should be decided on the basis of the scientific objectives of the study, with adjustments for the response of animals under the conditions prevailing at the laboratory (Tjølsen et al. 1992; Sawynok and Liu 2003). For ethical reasons, the lowest possible concentration of formalin consistent with scientific objectives should be used.

Dubuisson and Dennis (1977) quantified formalin nociception using a \textit{weighted-scores technique} (WST), which involves assigning weights to each behavioral category measured (paw favoring, paw elevation, or licking, biting, or shaking of the paw) (Figs. 1, 2a). The ordinality and validity of the category weights in the WST have been well established in rats (Coderre et al. 1993; Abbott et al. 1995). Others have used single behavioral scoring methods,
including recording of the time spent licking/biting the injected paw (Hunskaar et al. 1985) or counting the number of flinches (Wheeler-Aceto and Cowan 1991) (Fig. 2b), or have used automated scoring techniques (Jourdan et al. 2001). Parametric analysis suggests that the WST is superior to any single nociceptive measure; however, it is clear that assessment of paw favoring adds little to the equation and may be omitted from the analysis (Abbott et al. 1995). Paw licking/biting scores are commonly used in the mouse formalin test, since these behaviors predominate in mice and are easily quantified. It has been argued that ▶ flinching is more robust and less influenced by treatments affecting other behaviors (e.g., motor function), while licking/biting is regarded as being more variable and subject to motor influences, stereotypy, and perhaps taste aversion following earlier licking episodes (Wheeler-Aceto and Cowan 1991). Flinching and licking/biting may reflect distinct neuronal mechanisms, as they can be differentially modulated by certain drugs and procedures (e.g., amitriptyline and naloxone decrease licking/biting behaviors while simultaneously increasing flinching behaviors) (Sawynok and Liu 2003).

Concerning validation, the formalin concentration-response relationship, and the analgesic effects of opioids, has been examined for most scoring methods. However, few studies have determined whether nociceptive scores are suppressed by drugs known not to be analgesic in humans. The latter is particularly important, because sedation and other toxic effects can appear as analgesia. When different behaviors compete (e.g., a rat cannot favor its paw at the same time as licking it), then the interpretation of the change depends on whether one behavior represents greater nociception than another. This is problematic for some scoring methods, because a decrease in a behavior considered to represent greater nociception may occur because of drug side effects (Abbott et al. 1995). On the other hand, the selection of scoring method may also depend on other factors, such as the drug administration method. For example, in some cases, the presence of a chronic intrathecal (I.T.) cannula can eliminate the expression of licking/biting behaviors, yet leave flinching unaltered. This may be the reason why studies using rats and chronic I.T. cannulas (PE-10 tubing) generally do not report licking/biting behaviors as an outcome, yet when drugs are given spinally by acute lumbar puncture, such behaviors are often reported (Sawynok and Reid 2003).

An important characteristic of the formalin test is that there are two distinct phases of nociceptive behavior, described as the early and late, or first and second, phases. The early phase lasts 5–10 min; this is followed by a quiescent interval of 5–10 min, and then a subsequent late phase of activity is observed up to 60–90 min. The biphasic response to formalin is prominent in rats and mice, regardless of the nociceptive scoring method (i.e., WST, flinches, licking/bit- ing, or automated) (Fig. 2), but is less obvious in other species (Tjølsen et al. 1992). The biphasic nature of the formalin response is also observed for heart rate and blood pressure (Taylor et al. 1995), as well as the neuronal activity of Aδ- and C-fiber sensory afferent neurons (Puig and Sorkin 1995) or deep dorsal horn neurons of the spinal cord (Dickenson and Sullivan 1987) (Fig. 3). The two phases of nociceptive activity likely reflect an initial direct activation of nociceptive primary affere nts (i.e., nociceptors) by formalin, followed by afferent activation produced by inflammatory mediators released following tissue injury (Dubuisson and Dennis 1977; Tjølsen et al. 1992). The late phase may also involve ▶ central sensitization (Coderre 2001). A quiescent interval in C-fiber and dorsal horn neuron activation (Puig and Sorkin 1995; Dickenson and Sullivan 1987) tends to support the notion that distinct mechanisms underlie the two phases of behavioral and electrophysiological activation. However, the “interphase” also reflects ▶ active inhibition initiated by processes activated in phase 1. For example, a second formalin injection, administered 20 min after the initial injection, produces inhibition of behavioral responses and electrophysiological activity, with a time frame that corresponds to the first interphase interval (Fig. 4) (Henry et al. 1999).
Electrophysiological and pharmacological studies suggest that the early-phase formalin response depends on both the direct activation of nociceptors and neurogenic inflammation generated by the release of bradykinin, 5-hydroxytryptamine, histamine, and adenosine triphosphate (Tjølsen et al. 1992; Sawynok and Liu 2003). Formalin might also disrupt the perineurium, and this could enhance the access of tissue mediators to the sensory nerve. The late-phase formalin response depends in part on neurogenic inflammation induced by the above mediators as well as inflammatory responses associated with the release of cytokines and breakdown of arachidonic acid (Tjølsen et al. 1992; Sawynok and Liu 2003). There is also evidence to suggest that substance P- and glutamate-mediated central sensitization, initiated during the early phase, contributes to nociception in the late phase of the formalin test. This evidence arose from observations that the spinal administration of local anesthetics, opioids, and substance P or glutamate (N-methyl-D-aspartate) receptor antagonists inhibits late responses when given prior to, but not after, the early phase (Dickenson and Sullivan 1987; Coderre 2001). These findings have prompted the extensive use of the formalin test as an animal model for examining the potential of treatments for producing preemptive analgesia. The mechanisms underlying the active inhibition during the interphase are not completely understood but probably depend on both spinal

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**Formalin Test, Fig. 3** Time course of (a) mean C-fiber responses in sural nerve and (b) an individual dorsal horn (DH) convergent neuron response to hindpaw formalin injections of 5% formalin in rats. Note the biphasic nature of neuronal responses in both C-fibers and DH neurons (Modified with permission from (a) Puig and Sorkin (1995) and (b) Dickenson and Sullivan (1987))

**Formalin Test, Fig. 4** Effects of one or two injections (20-min interinjection interval) of 2.5% formalin into the plantar surface of one hindpaw on nociceptive scores in the formalin test. Filled triangles show the typical biphasic nociceptive response to a single injection. Open triangles show the effects of two injections of formalin. Note the second inhibitory interphase after the second formalin injection in the group that had two injections (Modified with permission from Henry et al. (1999))
and supraspinal influences, since the interphase is still present in spinalized animals but is eliminated by brain transection at the mesencephalic-diencephalic junction. A role for GABA_{A} receptors is suggested because the interphase is reduced both by spinal administration of GABA_{A} receptor antagonists and by systemic administration of low doses of barbiturates (Sawynok and Liu 2003).

While release of inflammatory mediators contributes to formalin-induced nociception, inflammation alone is not sufficient to produce the nociceptive behaviors induced by formalin. Thus, injection of inflammatory agents such as yeast, carrageenan, or Complete Freund’s Adjuvant (CFA) into the hindpaw produces profound edema but essentially no nociceptive shaking, licking, or flinching behaviors as produced by formalin. This implies that activation of nociceptors is a complex process that is to some extent dissociable from inflammatory processes (Sawynok and Liu 2003). Importantly, the inflammatory response to formalin, and the reliance of nociceptive response on inflammation, depends significantly on the concentration and volumes of formalin administered. Assuming that injection volumes are similar, low concentrations of formalin (1–2.5 % formalin or less) produce very little plasma extravasation and edema, while greater concentrations (5 %) produce significant hindpaw inflammation, lasting for as long as 1 week after injection. In addition, studies using adult pretreatment with capsaicin (to desensitize TRPV1-expressing nociceptors) and anti-inflammatory drugs (to target nonneurogenic inflammation) suggest that low concentrations of formalin produce effects that depend on neurogenic inflammation, whereas greater concentrations of formalin depend on nonneurogenic inflammation (Sawynok and Liu 2003; Coderre 2001). With greater concentrations of formalin, it is also more difficult to demonstrate a role for central sensitization in the late phase. Thus, nociceptive behaviors produced by 1–2.5 % formalin, but not those produced by 3.75–5 % formalin, are sensitive to preemptive effects of spinal administration of local anesthetics (Coderre 2001). The evidence suggesting differing roles of neurogenic and nonneurogenic inflammation with low and high concentrations of formalin has been recognized in rats, but not mice. However, it should be noted that the relatively large volumes of formalin injections typically used in mice produce significant inflammation even at low concentrations of formalin (reflecting different injection to tissue volume ratios) and might not allow for such a clear distinction.

Recent studies using knockout mice provide further insights into molecular mechanisms involved in formalin activation of nociceptors. In vitro data indicates that formaldehyde activates TRPA1 receptors, which is supported by complementary in vivo data that TRPA1-deficient (−/−) mice exhibit markedly reduced behavioral responses to formalin (Macpherson et al. 2007; McNamara et al. 2007). However, the attenuation of nociceptive responses is seen only at a low concentration of formalin (0.5 %), and there are no differences in responses at greater concentrations of formalin (2 % and 5 %) which are used more commonly in nociceptive behavioral tests (Bráz and Basbaum 2010). At the lower concentration, most formalin-responsive afferents are unmyelinated, but greater concentrations recruit both unmyelinated and myelinated afferents (Bráz and Basbaum 2010). The involvement of myelinated afferents in greater concentrations of formalin-induced behaviors is further supported by observations that ablation of the vast majority of C-fiber nociceptors does not alter such responses (Shields et al. 2010). Nerve injury occurs following administration of formalin, even at 0.5 %, as all concentrations of formalin lead to induction of activating transcription factor 3 (ATF3), a reliable marker of nerve injury (Bráz and Basbaum 2010). Hindpaw inflammation produced by CFA did not induce ATF3, and carrageenan led to only a slight effect; these observations suggest that nerve damage, not increased activity in nociceptors, resulted in ATF3 induction (Bráz and Basbaum 2010).

Formalin injections also activate processes that lead to long-term changes in the central
nervous system. Formalin injections lead to the spinal activation of various intracellular signaling molecules, such as cyclic-adenosine monophosphate (cAMP), protein kinase C, nitric oxide, cyclic-guanosine monophosphate (cGMP), mitogen-activated protein kinase (MAPK), cAMP-response element binding protein (CREB), as well as proto-oncogenes and their protein products, including c-fos, c-jun, Krox-24, Fos, Jun B, and Jun D. Formalin injections also produce delayed activation of microglia in spinal cord dorsal horn. These changes may underlie long-term changes in mechanical and thermal sensitivity that occur in sites adjacent to or remote from the injection site, which last from days to weeks after the injection (Sawynok and Liu 2003; Coderre 2001).

Cross-References

► Behavioral Studies in Animals
► Cingulate Cortex
► Nociceptive Processing in the Hippocampus and Entorhinal Cortex, Neurophysiology and Pharmacology

References


Forty Hz Oscillations

Definition

40 Hz activity is oscillatory activity described in the brain when the organism is actively engaged in a task.

Cross-References

▶ Corticothalamic and Thalamocortical Interactions

Fos Expression

Definition

The expression of Fos protein, the gene product of the c-Fos gene. Fos expression in a particular set of central nervous system neurons is often taken to indicate activity of that set of neurons in response to a noxious stimulus.

Cross-References

▶ Visceral Pain Model, Lower Gastrointestinal Tract Pain

Fos Protein

Definition

Fos is the protein that is expressed by the c-Fos gene in nociceptive neurons after noxious stimulation. Fos protein is found in the nucleus, where it serves as a transcription factor (third messenger).

Cross-References

▶ c-fos
▶ Spinal Cord Injury Pain Model, Contusion Injury Model
▶ Spinal Dorsal Horn Pathways, Dorsal Column (Visceral)
▶ Spinothalamic Tract Neurons, Role of Nitric Oxide

Fractalkine

Definition

Fractalkine is a cell-surface protein expressed by neurons in the spinal cord. When sufficiently activated, spinal neurons release fractalkine, which then binds to receptors expressed on microglia, thereby inducing the release of the proinflammatory cytokine interleukin (IL)-1. Peri-spinal administration of fractalkine, as well as IL-1, induces exaggerated pain responses. Importantly, inhibiting fractalkine activity blocks neuropathic pain, implying that endogenous fractalkine generates enhanced pain responses.

Cross-References

▶ Cord Glial Activation

Fractalkine (CX3CL1)

▶ Cathepsin and Microglia

Free from Bias

Definition

A personal attitude that may influence the evaluation of patients’ pain conditions or the
interpretation of study results. Pain measures should be bias-free in that children should use them in the same manner regardless of differences in how they wish to please adults.

Cross-References

▶ Pain Assessment in Children

Free Magnitude Estimation

Definition

Free magnitude estimation is the numerical rating of sensation magnitude without upper or lower boundaries.

Cross-References

▶ Opioids, Effects of Systemic Morphine on Evoked Pain

Free Nerve Endings

▶ Non-corpuscular Sensory Endings

Freeze Lesion

Definition

A brief punctual freeze lesion of human skin that causes moderate burning or itching sensations together with a reddening and a short-lived edema, after 24 h hyperalgesia to punctuate stimuli, hyperalgesia to blunt pressure and impact stimuli, and increased heat sensitivity. Brush-evoked hyperalgesia does not develop after freezing.

Characteristics

Injury of the skin is often followed by augmented pain sensations to mechanical, thermal, or chemical stimuli. Since the mechanism of the induction and maintenance of the different types of hyperalgesia are areas of considerable interest, scientists have searched for adequate experimental models, e.g., standardized lesions of the skin. Freeze injury of the skin was first described by...
Lewis and Love in 1926 (Lewis and Love 1926), maybe stirred by reports from expeditions to the North Pole in this decade, describing freeze injuries of their fingers and feet.

**Experimental Procedures**

Experimental inflammation by freezing the skin is normally induced on the upper leg, the forearm, or the back of the hand. For this purpose a cylindrical copper bar with a standardized diameter and weight (e.g., 15 mm and 290 g, respectively) is cooled to $-28^\circ$C (Kilo et al. 1994). This bar is placed on the skin, with its long axis perpendicular to the surface and a contact pressure provided by its weight. To improve thermal contact to the skin, saline-soaked filter paper is placed on the skin beneath the copper bar. The degree of developing inflammation is determined by the temperature of the copper bar and the thawing time of the lesioned skin site. The duration of freezing assessed that thawing duration normally account as to 20–40 s. Sensory testing for different forms of hyperalgesia follows 22–24 h after freezing the skin.

**Early Skin Reactions and Activation of Primary Afferents**

Volunteer subjects describe freezing of the skin as moderately painful, with sensations of electric prickling or slight itching. Intense burning sensations are reported rarely. At the lesioned skin site, a sharply delineated region of local reddening develops, due to both cold-induced vasodilatation and local edema which subside within 1–2 h (Lewis and Love 1926; Kilo et al. 1994). Freezing itself obviously provokes relatively little spontaneous activity in superficial nociceptors because they are rapidly inactivated by the decrease in skin temperature. Before inactivation by freezing Ad and C-nociceptors respond to noxious temperatures down to about $-10^\circ$C with graded responses. Units are recruited progressively with decreasing temperature and are thus suited to contribute to the sensation of cold pain (Simone and Kajander, 1996; Simone and Kajander, 1997; Campero et al. 1996). The obviously brief activation of nociceptors is reflected by a very spatially limited region of neurogenic inflammation around the frozen skin, since no flare or wheal reaction can be observed. For transduction of cold stimuli, different mechanisms have been proposed: activation of transient receptor potential channels, namely, TRPA1 and TRPM8, or inhibition of background potassium channels (Belmonte et al., 2009; Foulkes and Wood, 2007). Further on also a TTX-resistant sodium channel NaV1.8, which does not inactivate while cooling, is particularly important to retain excitability while cooling (Zimmermann et al., 2007).

The destruction of the cells in the upper skin layers evokes a complex inflammatory process, responsible for the altered pain sensation developing within the first day after freezing the skin.

**Activation and Sensitization of Nociceptive Spinal Cord Neurons**

Nociceptive spinal dorsal horn neurons respond to freeze injury of the skin. Both wide dynamic range (WDR) and nociceptive specific neurons (NS) are stimulated when the skin temperature in their innervation territories is lowered to $-15^\circ$C (Khasabov et al. 2001). WDR and NS neurons respond with a high-frequency discharge at the onset of freezing and subsequent ongoing activity. Moreover, a cross-sensitization by freezing of heat and cold activation thresholds is observed. Although little is known about the specific subtypes of peripheral afferents that excite the WDR and NS neurons, it is known that both types of dorsal horn neurons contribute to the cold and heat hyperalgesia produced by freeze injury. In a rat model, freezing the skin of the hindpaw also leads to increased c-fos expression in the spinal cord (Abbadie et al. 1994; Doyle and Hunt 1999).

**Heat Hyperalgesia**

Heat hyperalgesia, for instance, that following capsaicin application, is restricted to the primary hyperalgesic zone, and the underlying mechanism responsible for this is a peripheral sensitization of polymodal, mechano-heat sensitive, mostly unmyelinated nociceptors (Treede et al. 2004; Ali et al. 1996). Similarly heat hyperalgesia is observed at the injured skin site after freezing (1$^\circ$ zone) and to a minor extent also
in the 2° zone. The peripheral sensitization of heat sensitive ion channels such as TRPV1 – which is expressed in these nerve fibers – by locally released inflammatory mediators is responsible for the increased heat sensitivity after freeze lesion (Patapoutian et al. 2003). The sensitization to heat stimuli of spinal nociceptive neurons after freeze injury has also been demonstrated in rat and thus contributes to the development of heat hyperalgesia (Khasabov et al. 2001).

Patterns of Mechanical Hyperalgesia
After freezing the skin a characteristic pattern of mechanical hyperalgesia develops to punctuate stimulation (pin-prick hyperalgesia), to pressure stimulation, and to impact stimulation of the treated skin area. Increased sensitivity to non-noxious mechanical stimulation (brush-evoked; Alldynia) is not observed. The alterations of sensitivity to different types of mechanical stimuli at the site of the freeze injury (primary zone or 1°) and the area surrounding the site of injury (secondary zone or 2°) are described as follows:

Brush-Evoked Hyperalgesia
Brush-evoked hyperalgesia or allodynia (formerly also called hyperesthesia), normally occurring in the 1° and 2° zone, is not consistently found in the 2° zone and only rarely found in the 1° zone of the freeze model (Kilo et al. 1994). Mechanical alldynia is mediated by an enhanced central processing of normal sensory input coming from myelinated, mecano-sensitive A fibers (Ab fibers) that transmit non-painful, tactile sensations (Torebjork et al. 1992; Treede et al. 2004). Alldynia after capsaicin application is found in the primary and secondary hyperalgesic zone and results from central plasticity induced and sustained by persistent nociceptor activity from the primary zone. After freezing no psychophysiological correlate of Ab fiber activation is reported, suggesting that a lack of activity of Ab fibers together with the limited ongoing activity of nociceptors may explain the lack of alldynia.

Pin-Prick Hyperalgesia
Pin-prick hyperalgesia tested by punctuate stimulation of the skin develops in the primary and secondary zone after freezing the skin in a manner very similar to the pattern of pin-prick hyperalgesia observed after capsaicin application (Kilo et al. 1994). In the 1° zone a sensitization of C-nociceptors to mechanical stimulation leads to an increased input to the spinal cord. Astonishingly only a few studies have shown a peripheral sensitization of C or Ad fibers to suprathreshold mechanical stimuli, and mechanical activation thresholds remained unchanged (Cooper et al. 1991; Schmelz et al. 1996). However, the normally mecano-insensitive class of nociceptors is sensitized by repeated mechanical stimulation and could contribute to the primary mechanical hyperalgesia (Schmidt et al. 2000). Which fiber types contribute to the central sensitization resulting in the pin-prick hyperalgesia in the freeze model is not clear, but after triggering the central sensitization, no ongoing activity of these nociceptors is required. The hyperalgesia in the 2° zone surrounding the injured skin site is also caused by central sensitization following excitation of C or Ad nociceptors in the injured area that facilitate Ad fiber input from the unlesioned secondary zone.

Hyperalgesia to Impact Stimuli
C and Ad fiber nociceptors are able to encode impacts of different strengths and after sensitization these fibers mediate hyperalgesia to impact stimuli (Koltzenburg and Handwerker 1994). The freezing lesion, in contrast to capsaicin application, induced this special type of hyperalgesia in the primary zone (Kilo et al. 1994). Maybe due to a long lasting and severe inflammatory tissue damage, that again induces the sensitization of mechano- and/or polymodal nociceptors.

References


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**Frequency of Low Back Pain**

- **Low Back Pain, Epidemiology**

**Frequency of Ultrasound Treatment**

**Definition**

The most commonly used frequencies are in the range of 0.8–1.1 MHz, although frequencies around 3.0 MHz are also fairly common.

**Cross-References**

- **Ultrasound Therapy of Pain from the Musculoskeletal System**

**Frequency-dependent Nociceptive Facilitation**

- **Windup of Spinal Cord Neurons**

**Freund’s Complete Adjuvant**

**Synonyms**

- FCA

**Definition**

Freund’s complete adjuvant (FCA) is a suspension of heat-killed mycobacterium in neutral oil, usually paraffin or mineral oil. Suspension is often achieved by ultrasonication.
Friction Massage

Definition

Frontal-posterior neck electromyographic sensor placement is an approach designed to assess muscle activity across a broad region, ranging from the back of the neck to the front of the head.

Cross-References

▶ Massage, Basic Considerations

Functional Abdominal Pain

Definition

The term “functional abdominal pain” (FAP) refers to chronic or recurrent abdominal pain that cannot be explained by any lesion, change in structure, or derangement of an organ.

Synonyms

Chronic abdominal pain; Recurrent abdominal pain (RAP)

Fulcrum

Definition

The fulcrum is a pivot about which a lever turns.

Cross-References

▶ Arthritis Model, Adjuvant-induced Arthritis

▶ Sacroiliac Joint Pain

▶ Friction

▶ Massage and Pain Relief Prospects

▶ Massage, Basic Considerations

▶ Friction Massage

▶ Psychophysiological Assessment of Pain

▶ Frustration

▶ Anger and Pain

▶ Functional

Definition

Functional is a term used before a symptom or disease to describe a process where a symptom or disease cannot be explained by any lesion, change in structure, or derangement of an organ.

Cross-References

▶ Functional Abdominal Pain in Children

▶ Functional Abdominal Pain

▶ Descending Modulation of Visceral Pain

▶ Visceral Pain Model, Irritable Bowel Syndrome Model

Functional Abdominal Pain in Children

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without evidence of a pathologic or organic condition. FAP is included as a diagnostic category among the childhood functional gastrointestinal disorders (FGID) as defined by the Rome criteria (Rasquin et al. 2006). FAP is considered a diagnosis of exclusion, with criteria only requiring the presence of episodic or continuous abdominal pain that is not better defined by another FGID or related to an organic process (e.g., anatomic, metabolic, infectious, or inflammatory disorder). FAP Syndrome is also described in the Rome Criteria, which requires the additional presence of disability related to pain (e.g., school absences) and other somatic symptoms (e.g., headache). Within the Rome criteria, there are other pain-related FGIDs that are not defined as FAP because the presence of associated symptoms qualifies as a separate diagnosis. For example, Irritable Bowel Syndrome (IBS) is defined as abdominal pain associated with changes in and relief by bowel movements. As a result, clinically, FAP typically describes a small number of FGID patients with abdominal pain. However, in the research setting, it is more common for FAP to be used as a term to describe abdominal pain conditions that are not associated with organic disease in general.

Introduction

Abdominal pain is a common complaint of childhood. Originally identified in the pediatric literature in the 1950s, “recurrent abdominal pain” was defined as abdominal pain severe enough to interfere with normal activities (Apley and Naish 1958). It was described as a common occurrence among school-aged children, with a greater prevalence in females than males (Apley 1975). More recent population studies have found that it is common for children to experience abdominal pain at some point during development, with up to 43 % of school children reporting transient abdominal pain (Roth-Isigkeit et al. 2005) and 10–15 % of children reporting chronic abdominal pain problems (Liakopoulou-Kairis et al. 2002). Studies of FAP prevalence among pediatric patients in the medical setting have shown that 2–4 % of all pediatric primary care patients are seen for abdominal pain complaints and up to 50 % of pediatric gastroenterology patients have a pain-related FGID (Nurko and Di Lorenzo 2008).

From a biological standpoint, FAP is understood to be a physiological disorder generated by a combination of disruptions in intestinal and central nervous system activity (Chiou and Nurko 2010). Changes in intestinal motility can result in painful muscular spasms and contractions. Visceral hypersensitivity, a result of nerves in the gastrointestinal (GI) tract becoming over sensitized, contributes to the production of pain or discomfort from normal stimuli. Finally, communication between the brain and gut becomes dysregulated, resulting in increased pain signaling and perception.

From a psychosocial standpoint, disturbances in mood and functioning amplify illness experience and adversely affect health status for patients with FAP. FAP is disruptive to normal childhood development. FAP is associated with anxiety, depression, and somatic symptoms; in addition, FAP is associated with high levels of functional disability, school absence, and health care utilization (Campo et al. 2004).

Because of the complex relationship between these factors that contribute to the presentation of FAP, it is widely agreed that FAP is best understood through a biopsychosocial model (Chiou and Nurko 2010). The biopsychosocial model “integrates biological science with the unique features of the individual and determines the degree to which biological and psychosocial factors interact to explain the disease, illness, and outcome” (Drossman 1998, p. 262). In addition to the biological process, psychological, social, environmental, and behavioral factors also are recognized as potential contributing and interacting factors in patients’ experience of FAP. It is equally important to assess and treat FAP from a broad perspective. Research has identified several factors that may predispose a child to develop FAP. Genetics play a role in making it more likely for a child to develop
physiological disruptions in the GI tract (Talley 2008). Early life events, such as premature birth or early medical procedures, have been identified as potential precursors to the development of visceral hypersensitivity (Miranda 2008). Parent and family factors also play an important role; there is a clustering of chronic pain in families that may occur through parental modeling of illness behavior and/or through shared genetics (Levy et al. 2000).

**Characteristics**

Many studies have been conducted to examine concurrent and long-term medical and psychosocial outcomes in children with FAP. Pediatric FAP patients demonstrate more anxious, depressive, and somatic symptoms, experience more stressful life events, and have more school absences than well children (e.g., Campo et al. 2004; Walker et al. 1993; Walker and Greene 1989). Furthermore, children with FAP have increased depression, more somatic symptoms, and greater functional impairment compared to children with organic gastrointestinal disease (Walker et al. 1991). A long-term follow-up study demonstrated that patients with FAP continued to have more abdominal pain episodes, greater disability, more functional impairment, and greater health service utilization 5 years after initial evaluation compared to a well sample (Walker et al. 1995). In the same study, examination of patients’ subsequent medical diagnoses revealed that only 1 child out of 31 was later diagnosed with an organic condition that may have accounted for his or her symptoms. A recent study of adults who had FAP as children found that one third continued to have abdominal pain into adulthood, in addition to the development of other chronic pain conditions (Walker et al. 2010).

Studies of parents of children with FAP have revealed a high level of anxiety (Garber et al. 1990) as well as a strong history of FGIDs (Levy et al. 2000) compared to parents of well children. Parents of children with FAP typically report high levels of distress about their children’s symptoms, such as describing themselves as helpless in dealing with their children’s pain and identifying threat of serious disease as their most central concern (Van Tilburg et al. 2006). These factors may lead parents to reassure their children and protect them from harm by encouraging children to withdraw from activities. Although parents have good intentions, this type of protective parenting behavior has been associated with high levels of school absence and pain-related disability in pediatric FAP patients (e.g., Walker and Zeman 1992). In contrast, distracting or coping-promoting parenting behavior that draws children’s attention away from symptoms and encourages participation in regular activities is associated with fewer symptom complaints and better psychosocial outcomes among children with FAP (e.g., Walker et al. 2006).

**Treatment**

Several interventions have been found to be effective for treating FAP. As stated, it is essential that FAP is assessed and treated from a biopsychosocial model to ensure that all factors that contribute to the FAP presentation are addressed.

Medical therapies typically include dietary changes to improve motility (e.g., increased fiber intake), medication from the tricyclic antidepressant or selective serotonin reuptake inhibitor classes to regulate visceral hypersensitivity and the brain-gut pathway (e.g., amitriptyline, citalopram), and other common GI therapies to regulate the digestive system as a whole (e.g., antacid or proton pump inhibitor therapies, supplements such as peppermint oil). Regulating the GI system from the biological standpoint can help decrease pain and discomfort and is one of the essential features of treating FAP (Nurko and Di Lorenzo 2008).

Psychological therapies have been found to have a promising evidence base for pediatric FAP. Treatment typically involves cognitive
behavioral therapy (CBT) performed individually with the child, or with the child and family. The goal of CBT is for children to learn pain coping skills (e.g., relaxation techniques, positive thinking strategies) and adopt a functional pain coping approach (e.g., adopting active and distracting pain coping skills to continue with regular activities). Even if a child is seen for individual therapy, it is essential for the treating provider to work with the child’s school and family to ensure that the functional pain coping approach is supported in the larger system. Another modality of psychological therapy is biofeedback, consisting of focused relaxation practice that helps children restore physiological balance to their bodies, which has also been associated with improvements in pain and functioning among children with FAP (Schurman et al. 2010). A recent review of psychological therapies for youth with chronic pain found that cognitive behavioral therapy and relaxation techniques are effective in reducing pain severity and frequency, as well as have a lasting effect for symptom improvement (Eccleston et al. 2009).

Summary

FAP is a common complaint of childhood that has been extensively studied in the literature. FAP is a physiological disruption of the GI tract in the absence of organic disease. Pediatric FAP patients experience high levels of disability and psychological distress. Furthermore, many patients who experience FAP as children report higher levels of pain, functional disability, and health service utilization as adults, and a significant proportion go on to develop other chronic pain problems. From a biopsychosocial perspective, the role of central sensitization of pain perception in the brain, in addition to ongoing psychological and social stressors, likely combine to influence maintenance or persistence of pain. These negative concurrent and long-term emotional and behavioral outcomes underscore the significant potential impact of FAP on children’s lives and futures, adding to the importance of improving the understanding and treatment of patients with these conditions through a biopsychosocial approach.

References


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### Functional Aspects of Visceral Pain

- [Psychiatric Aspects of Visceral Pain](#)

### Functional Bowel Disorder

**Definition**

Functional bowel disorder is a disorder or disease where the primary abnormality is an altered physiological function (the way the body works) rather than an identifiable structural or biochemical cause. A functional disorder does not show any evidence of an organic or physical disease. It is a disorder that generally cannot be diagnosed in a traditional way, as an inflammatory, infectious, or structural abnormality that can be seen by commonly used examination, x-ray, or laboratory test.

### Cross-References

- [Descending Modulation of Visceral Pain](#)
- [Visceral Pain Model, Irritable Bowel Syndrome Model](#)

### Functional Brain Imaging

**Definition**

Functional brain imaging is a noninvasive neuroimaging technique that detects changes in brain metabolism or neuronal activity in response to sensory, motor or cognitive tasks, giving information regarding the function of specific brain regions; see also [functional imaging](#) and [fMRI](#).

### Cross-References

- [Thalamus and Visceral Pain Processing (Human Imaging)](#)
Functional Capacity

Definition

For United States Social Security purposes, functional capacity represents the measure of a person’s ability to perform particular work-related physical and mental activities.

Cross-References

▶ Disability Evaluation in the Social Security Administration

Functional Capacity Assessment

▶ Disability, Functional Capacity Evaluations

Functional Capacity Battery

▶ Disability, Functional Capacity Evaluations

Functional Capacity Evaluation

Synonyms

FCE

Definition

Functional capacity evaluation systematically measures the worker’s ability to carry out work tasks safely. It includes trait-oriented systems of norm-referenced assessment, e.g., the Baltimore Therapeutic Equipment (BTE) (http://www.bteco.com/). The results demonstrate the individual’s physical functional capacity, e.g., lifting capacity, fine motor dexterity, work tolerance, and preparedness for returning to work.

FCE has been criticized for the lack of correspondence between the individual’s functional capacity and a job’s real requirements: It does not demonstrate the individual’s opportunities of returning to, and retaining, a job. Synonyms: physical capacity evaluation; work capacity evaluation.

Cross-References

▶ Disability, Functional Capacity Evaluations
▶ Vocational Counseling

Functional Changes in Sensory Neurons Following Spinal Cord Injury

▶ Disability, Functional Capacity Evaluations

Functional Changes in Sensory Neurons Following Spinal Cord Injury in Central Pain

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Synonyms

Central pain; Functional changes in sensory neurons following spinal cord injury

Definition

Chronic pain is a common consequence of spinal cord injury (SCI), often mixed with
nociceptive, visceral, and neuropathic components. Neuropathic SCI pain is a form of central pain that represents a major challenge for those responsible for clinical pain management (Siddall et al. 2002). Several models of SCI have been developed in recent years that allow the direct examination of neuronal mechanisms mediating SCI-induced central pain (Vierck et al. 2000).

Central pain refers to neuropathic pain associated with a lesion of the central nervous system. Spinal cord injury pain (SCI pain) is a particular form of central pain seen in patients with spinal cord injury or diseases of the spinal cord, e.g., syringomyelia and tumors. The dorsal horn of the spinal cord is the first relay point for somatosensory perception. Neurons in the dorsal horn process sensory input and transmit this information to higher brain centers, while initiating motor and autonomic reflexes. Sensory neurons in the dorsal horn can be classified into three types with respect to responses to mechanical stimulation: low-threshold (LT) neurons that respond maximally to innocuous stimuli, wide dynamic range (WDR) neurons that give graded responses to innocuous and noxious stimulation, and high-threshold (HT) neurons that respond exclusively to noxious stimulation.

Introduction

Chronic pain is a common consequence of spinal cord injury (SCI), often mixed with nociceptive, visceral, and neuropathic components. Neuropathic SCI pain is a form of central pain that represents a major challenge for those responsible for clinical pain management (Siddall et al. 2002). Several models of SCI have been developed in recent years that allow the direct examination of neuronal mechanisms mediating SCI-induced central pain (Vierck et al. 2000).

Characteristics

In recent years, several studies have been published characterizing the response patterns of dorsal horn neurons in rats with spinal cord injury and behaviors suggesting the presence of SCI pain. The models of injury employed include photochemically induced ischemic SCI (Hao et al. 1992; Hao et al. 2004), excitotoxicity associated with intraspinal injection of quisqualic acid (Yezierski and Park 1993), contusion (Drew et al. 2001; Hoheisel et al. 2003; Hains et al. 2003a), transection (Scheifer et al. 2002; Zhang et al. 2005), and hemisection (Hains et al. 2003b; Lu et al. 2008). Below are described four functional characteristics of dorsal horn neurons that have been described as changing following spinal cord injury.

Receptive Fields

The proportion of dorsal horn neurons without a demonstrable mechanical receptive field (RF) is increased after spinal cord injury (Hoheisel et al. 2003; Hao et al. 2004). These neurons tend to have high-frequency ongoing activity and are clustered around the rostral end of the injured spinal segment. This suggests that the normal afferent input (either direct or indirect) to some of these neurons has been interrupted by injury, resulting in a lack of RF. The original RFs of these neurons are likely to be on skin areas rendered anesthetic by the injury. Abnormal spontaneous discharges of these neurons, especially those projecting to higher centers, may give rise to dysesthesia or pain referred to the anesthetic skin areas caudal to the lesion. This type of pain is referred to as below level pain and is a major component of the pain syndrome in patients with SCI (Siddall et al. 2002). There are also behavioral indications of below level pain in rat models in the form of autotomy and excessive scratching/grooming leading to skin damage (Vierck et al. 2000).

Spontaneous Activity

In our analysis of activity of dorsal horn neurons after SCI, we have described animals with segmental allodynia, and these rats have a larger proportion of neurons with high rates of spontaneous activity (SA) (Hao et al. 2004). These neurons were located near the edge of the lesion site. This is similar to the results of
Hoheisel et al. (2003) and Zhang et al. (2005) who found that neurons close to a spinal contusion or transection exhibited increased levels of ongoing activity. Yezierski and Park (1993) and Drew et al. (2001) have also reported a higher level of such activity in neurons in spinally injured rats. In our sample, the level of spontaneous activity of HT neurons and neurons without receptive fields was significantly higher than that of LT or WDR neurons. Interspike interval analysis indicated that the discharges were irregular and burst-like in the majority of SA neurons. Since HT neurons receive input from nociceptors and are involved in pain signaling (Chung et al. 1986), the high rate of SA in HT neurons may give rise to spontaneous pain sensations in skin areas with sensory loss. Hoheisel et al. (2003) have also noted several forms of pathophysiological background activity that were not seen in normal animals, including bursting-like activity.

Changes in the Functional Type of Neurons Recorded

In normal rats, the proportion of different neuronal types recorded depends on several factors, including classification criteria used, type of preparations, anesthesia, etc. In our study, we used an intact rat preparation with urethane anesthesia and we recorded from neurons with response characteristics resembling those of LT, WDR, and HT neurons (Chung et al. 1986). The relative proportion of these neuronal types in a sample of normal rats was similar to that reported in most previous studies in the field. By contrast, considerably more WDR neurons were encountered in spinally injured rats two to three segments above the injury (Hao et al. 2004). Since neurons in normal and injured rats were recorded from different animals, it is impossible to know the original phenotype of these WDR neurons. We have speculated that the increased proportion of WDR neurons reflects either the appearance of novel innocuous input to HT neurons or increased responses of LT neurons to noxious input. Both possibilities imply that there is an increased excitability in sensory pathways in the spinal cord underlying behavioral allodynia. A decrease in inhibitory influences may also contribute to these functional changes. Drew et al. (2001) have also compared the response properties of neurons in normal, spinally injured non-allodynic and allodynic rats. Interestingly, they observed that the proportion of LT neurons was increased and they became more common than WDR neurons rostrally, but not caudally, to the lesion site. The difference between our results and those of Drew et al. (2001) may be due to differences in classification criteria, since they did not have HT neurons in their sample.

Responses to Peripheral Stimulation

Mechanical allodynia is a common symptom in patients with SCI pain (Siddall et al. 2002), and similar behavior is consistently observed in rat models of SCI pain (Xu et al. 1992; Vierck et al. 2000). In support of the behavioral observations, electrophysiological recording of dorsal horn activity in these animals has revealed increased neuronal responsiveness to mechanical stimulation. This included increased responses of WDR neurons to brush, pinch, and graded von Frey hair stimulation, decreased von Frey threshold, increased response of HT neurons, and increases in afterdischarges (Hao et al. 1992; Yezierski and Park 1993; Drew et al. 2001; Hains et al. 2003; Hoheisel et al. 2003; Zhang et al. 2005). These changes are likely to underlie the mechanical allodynia observed following spinal injury. Similarly, we have also found that the responses of dorsal horn neurons to cold stimulation increased after SCI, corresponding to cold allodynia in these rats. A higher percentage of WDR and LT neurons, which normally react poorly to cold, react to cold stimulation in allodynic rats (Hao et al. 2004).

Conclusions

Abnormal electrophysiological properties of dorsal horn neurons can be documented in rats with chronic pain-related behaviors after SCI. Based on the similarities between the neuronal and behavioral responses, it is likely that neuronal changes in the dorsal horn around the level of injury are responsible for the behavioral manifestation of pain-like responses. Some of the abnormalities
are most probably the result of deafferentation in the zone immediately rostral to the spinal lesion. The reduction of spinal GABAergic inhibition has also been shown to be involved in the mechanical hypersensitivity of dorsal horn neurons after SCI (Hao et al. 1992; Lu et al. 2008). Moreover, SCI induces complex neurochemical changes in areas rostral to the lesion, which may also contribute to the neuronal abnormalities. It is important to note that some of neuronal changes observed in spinally injured rats, noticeably spontaneous hyperactivity in the dorsal horn, have also been seen in patients with SCI pain and lesions of the dorsal root entry zone; targeting areas of spontaneous activity have been shown to alleviate pain (Falci et al. 2002).

References


Definition

Functional imaging is a general term used to describe methodologies that allow function to be located either spatially or temporally within the brain (and other organs). The methods allow detection of molecular signals that indicate the presence of biochemical activity and changes, such as cell activity or death. They are generally noninvasive and used for human studies. The term “neuroimaging” is often used when applied specifically to brain studies. Methods include: Functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET), Magneto-Encephalography (MEG), and Electro-Encephalography (EEG).

Characteristics

Functional imaging techniques applied for the study of cutaneous pain are ▶ positron emission tomography (PET), ▶ functional magnetic resonance imaging (fMRI), multi-lead electroencephalography (EEG), and ▶ magnetoencephalography (MEG). PET measures cerebral blood flow, glucose metabolism, or neurotransmitter kinetics. A very small amount of a labeled compound (called the radiotracer) is intravenously injected into the patient or volunteer. During its uptake and decay in the brain, the radionuclide emits a positron, which, after traveling a short distance, “annihilates” with an electron from the surrounding environment. This event results in the emission of two gamma rays of 511 keV in opposite directions, the coincidence of which is detected by a ring of photomultipliers inside the scanner. In case of the most common use of $\text{O}^{15}$-water injection, counting and spatial reconstruction of these occurrences within the brain anatomy allow visualization of the regional cerebral blood flow response (rCBF) as an indicator of neuronal activity. Usually scans during painful stimulation are statistically compared with scans during the resting state or non-painful stimulation (blocked design) and plotted as 3-dimensional color-coded $t$- or $Z$-score maps.

FMRI images blood oxygenation using the so-called BOLD (blood oxygen level-dependent) technique which exploits the phenomenon that oxygenated and deoxygenated hemoglobin possess different magnetic properties. Both the rCBF using $\text{O}^{15}$-water PET and the BOLD technique rely on neurovascular coupling mechanisms that are not yet fully understood, but which...
overcompensate local oxygen consumption, thus causing a flow of oxygenated blood into neuronally active brain areas in excess of that utilized.

EEG and MEG are noninvasive neurophysiological techniques that measure the respective electrical potentials and magnetic fields generated by neuronal activity of the brain and propagated to the surface of the skull where they are picked up with EEG-electrodes or, in the case of its magnetic counterpart, received by SQUID (supra conducting quantum interference device) sensors located outside the skull. Compared with PET and fMRI, EEG and MEG are direct indicators of neuronal activity and yield a higher temporal resolution of the investigated brain function. The spatial distributions of EEG potentials and MEG fields at characteristic time points following noxious stimulation (noxious stimulus) are analyzed using an inverse mathematical modeling approach called equivalent current dipole (ECD) reconstruction. An ECD evoked by painful stimuli hence represents a source model of pain-relevant activity within the brain. The spatial acuity of MEG is higher than that of EEG because the latter measures the extracellular volume currents that are distorted by the differentially conducting tissues such as gray and white matter, cerebrospinal fluid, durae, and bone. In contrast, MEG measures the magnetic field perpendicular to the intracellular currents undistorted by the surrounding tissue. Given the different geometry of electrical potentials and magnetic fields, MEG is predominantly sensitive to dipoles oriented tangentially to the head convexity, whereas EEG depends primarily on radial but also on tangential dipoles. Functional imaging using PET, fMRI, EEG, and MEG has substantially increased the knowledge about the cerebral representation of pain (Casey 1999) and its modulation by psychological phenomena (Porro 2003).

A bone of contention in the research field dealing with the cerebral representation of pain is the involvement of primary and secondary somatosensory cortex. When using contact heat to activate nociceptors, multiple areas of the brain such as the thalamus, primary (SI) and secondary (SII) somatosensory cortices, posterior and anterior parts of the insula, and mid-caudal parts of the anterior cingulate cortex (ACC) respond to this input in a correlated manner with perceived intensity (Coghill et al. 1999). However, the touch of the probe or attentional effects inherent in block designs could explain SI and SII cortex activity being unrelated to pain. Yet, if infrared laser stimuli that lack a concomitant tactile component are applied over a range of randomly presented intensities in event-related designs by MEG (Timmermann et al. 2001) or fMRI (Bornhoevd et al. 2002), SI activity shows a steady increase with laser heat intensity, whereas the SII and insula respond robustly to painful but not or only slightly to non-painful intensities. Using BOLD responses of FMRI, Moulton et al. (2012) recently compared different degrees of non-painful and painful contact heat intensities and found best correlation with heat rather than pain intensity in contralateral SI and SII cortices. Discrepancy between laser and contact heat may be due to the fact that laser stimuli involve a very narrow range of pre-pain intensities. These stimulus–response functions fit with the behavior of distinct wide dynamic range (WDR) and nociceptive-specific (NS) neurons of the dorsal horn, thalamus, and SI cortex (Price et al. 2003). These features and the importance of a relay of afferent activity in lateral thalamic nuclei substantiate the key role of SI and SII cortices as part of a lateral pain system subserving the sensory-discriminative function of pain (Melzack and Casey 1968; Price 2000). Under conditions of specific psychological interventions such as hypnosis (Rainville et al. 1997), pain anticipation (Ploghaus et al. 1999), or placebo cognitions (Petrovic et al. 2002), frontal brain regions such as ACC and the anterior insula appear to subserve more specifically the affective-motivational and cognitive component of pain (Melzack and Casey 1968; Price 2000). They represent the major targets of the medial pain system given a major afferent input to these brain areas from medial thalamic nuclei. Other areas such as basal ganglia, cerebellum, and various structures within the prefrontal cortex yielded activation by experimental pain in several studies; their role in pain processing,
however, remained elusive and is mainly deduced from their importance in other cognitive, motor, or behavioral functions.

Craig (2003) challenged the concept of a sensory-discriminative function of pain. An important component of his hypothesis is the assumption that pain is primarily an interoceptive perception like hunger, thirst, or itch, originating in specific spinothalamic tract (STT) neurons of the superficial dorsal horn (lamina I). As “labeled lines,” these STT neurons impinge upon specific thalamic nuclei, such as the posterior part of the ventromedial nucleus (VMpo) and the ventral caudal part of the mediodorsal nucleus (MDvc), which relay afferent input to dorsal posterior insula and caudal ACC, respectively. These two pathways are regarded as important elements of a hierarchical system subserving \( \text{homeostasis} \), linking the sense of the physiological condition of the body (\( \text{interoception} \)) with subjective feelings and emotion. Although the interoceptive function of pain is well conceivable, negation of an exteroceptive function of pain is neither intuitive nor supported by functional imaging data (see above). Word descriptors such as those compiled in the McGill Pain Questionnaire, e.g., cutting, pinching, stinging, squeezing or crushing, and many more, express how a stimulus from outside the body causes pain and are often used by pain patients to describe their pain, although there is no exteroceptive stimulus. In contrast, there is clearly less richness of exteroceptive sensory descriptors for hunger or thirst, even though the latter are much more everyday sensations or feelings than pain. Lenz et al. (2004) electrically stimulated thalamic termination areas of STT neurons in conscious patients undergoing stereotactic procedures for the treatment of movement disorders and chronic pain. Patients used mainly exteroceptive words, rarely internal or emotional phenomena, to describe their subjective responses to the stimuli. Furthermore, two groups of responses were observed following stimuli applied to distinct thalamic locations, a binary response signaling pain, but no non-painful sensation, and an analog response covering graded intensities across non-painful and painful sensations. This result is consistent with a sensory-discriminative or exteroceptive pain function through pathways that convey alarm according to an all-or-nothing stimulus–response relationship and others that indicate how strong and where the stimulus is.

The ambiguity of pain as exteroceptive or interoceptive phenomenon likely relates to the fact that many painful experiences throughout the entire life span of an individual derive from the skin (burns, cuttings, etc.). The human skin forms the interface between the body and the outer world. Cutaneous sensitivity is therefore primarily reflecting the capability of the organism to receive signals from outside the body in the form of touch, temperature, and pain sensations. As a consequence, cutaneous sensitivity primarily subserves an exteroceptive function. However, pathological changes of the skin due to inflammation or injury lead to pain that informs the individual about the body rather than a stimulus from the outer world and, therefore, serves an interoceptive function. Often the term interoception is attributed to visceral sensation, or homeostatic feelings such as hunger and thirst. Yet, inflammatory and injury pain of the skin are indeed good indications that a change in the bodily state can also involve a shift from primarily exteroceptive to interoceptive cutaneous pain function. Sound support for the hypothesis that cutaneous pain inherits both exteroceptive and interoceptive functions is provided by a PET imaging study conducted by Lorenz et al. (2002). These authors addressed the question of whether nociceptive activity resulting from two equally painful contact heat stimuli applied to normal skin or the same skin sensitized by a topical solution of capsaicin would yield different functional imaging results. They tested whether the effect of skin sensitization would be similar to that of pain intensity observed by the same group in an earlier study when painful heat was compared with non-painful warmth (Casey et al. 2001). Thus, whereas the critical aim of the Lorenz et al. experiment was to match subjective intensities of a slowly ramped and continuously applied contact heat stimulus across normal and sensitized skin conditions to minimize a confound
Functional Imaging of Cutaneous Pain, Fig. 1 Stimulus paradigms to differentially manipulate body-related (interoceptive) and stimulus-related (exteroceptive) pain processes with positron emission tomography (PET). The top section shows the temporal profile of two slowly ramped heat stimuli reaching different plateaus equated for subjective pain intensity. One stimulus is applied on the normal skin of the left volar forearm to approximately 47 °C (solid black), which is 2 °C above the average heat pain threshold (dotted black) and felt as a clear, but tolerable pain sensation. Another stimulus is applied to approximately 43 °C on the same skin, when it had been sensitized by a topical solution of capsaicin (solid red). This treatment caused a drop in the heat pain threshold by approximately 4 °C (dotted red), rendering the heat stimulus as painful as the 4 °C more intense stimulus applied on normal skin. The subtraction of PET scans between the two conditions (capsaicin-treated minus normal skin) is shown at the bottom of section A. Surface-rendered images and median sagittal cuts from both sides, a horizontal slice 11 mm above the AC-PC line, and a superior view are displayed. The images demonstrate activity of the midbrain, medial thalamus, anterior insula, perigenual cingulate, and prefrontal cortex representing the change in the physiological status of the skin (sensitized vs. normal). The bottom section shows the temporal profile of two heat stimuli that were set to a constant temperature of either 50 °C or 40 °C in different blocks and repeatedly applied to different spots of the normal skin, each contact lasting 5 s. Images comparing these two stimuli illustrate activity in the lateral thalamus, lenticular nucleus, mid-posterior insula/SII, mid-anterior cingulated, cerebellum, and premotor cortex, the latter extending into the MI/SI region.
with perceived intensity and test the importance of the physiological status of the tissue (interoception), the Casey et al. study tested the importance of different applied and perceived intensities of repeated rapidly ramped contact heat stimuli without changing the tissue status (exteroception). Their results illustrated in Fig. 1 show that interoceptive and exteroceptive manipulations of burning pain engage clearly different forebrain structures. Key structures responding to manipulating the exteroceptive stimulus condition are the lateral thalamus, lenticular nucleus/putamen, mid-posterior insula/SII, SI/MI, caudal ACC, premotor cortex, and cerebellum. In contrast, key structures responding to manipulating the interoceptive stimulus condition are the medial thalamus, ventral caudate/nucleus accumbens, anterior insula, dorsolateral prefrontal and orbitofrontal cortices, and the perigenual ACC. Notably, although the perceived intensities were equated between the two skin conditions in the Lorenz et al. study, pain on sensitized skin (heat allodynia) yielded greater negative affect according to ratings subjects made using both a visual analog scale of “unpleasantness” and a short form of the McGill Pain Questionnaire at the end of each scan. This result is consistent with the close relationship of interoception with emotion giving rise to intrinsically stronger affective pain experiences during pathological tissue states. Furthermore, the involvement of cerebral motor systems differs between exteroceptive and interoceptive pain. Whereas exteroceptive pain recruits brain structures such as the putamen, motor and premotor cortex, and cerebellum suited to govern an immediate and spatially guided defense or withdrawal due to their somatotopic organization (Bingel et al. 2004a, b), interoceptive pain engages the ventral caudate and nucleus accumbens, which are part of a limbic basal ganglia loop relevant for motivational drive of behavior rather than motor execution. Overall, these results substantiate suggestions that different projection systems originating in the dorsal horn of the spinal cord mediate normal pain and pain from sensitized nociceptors (Hunt and Mantyh 2001). In differentiating different pain types by their origins from either outside or inside the body, the brain may engage different behavioral adaptations according to the meaning of the pain in relation to the physiological status of the body.

References


### Functional Imaging of Descending Modulation

▶ Descending Circuits in the Forebrain, Imaging

### Functional Loss

**Definition**

Functional loss is a decrease or loss of physiological function.

**Cross-References**

▶ Disability, Upper Extremity

### Functional Magnetic Resonance Imaging

**Synonyms**

fMRI

**Definition**

Functional Magnetic Resonance Imaging (or fMRI) is the use of MRI to learn which regions of the brain are active in a specific cognitive task or during sensory stimulation, e.g., during a pain experiment. It is one of the most recently developed forms of brain imaging, and measures hemodynamic signals related to neural activity in the brain or spinal cord of humans or other animals. As nerve cells “fire” impulses, they metabolize oxygen from the surrounding blood. Approximately 6 s after a burst of neural activity, a hemodynamic response occurs and that region of the brain is infused with oxygen-rich blood. As oxygenated hemoglobin is diamagnetic, while deoxygenated blood is paramagnetic, MRI is able to detect a small difference (a signal of the order of 3 %) between the two. This is called a blood-oxygen-level-dependent, or “BOLD,” signal. The precise nature of the relationship between neural activity and the BOLD signal is a subject of current research.

**Cross-References**

▶ Amygdala, Functional Imaging
▶ Cingulate Cortex, Functional Imaging
▶ Descending Circuits in the Forebrain, Imaging
▶ Human Thalamic Response to Experimental Pain (Neuroimaging)
▶ Nociceptive Processing in the Nucleus Accumbens, Neurophysiology and Behavioral Studies
▶ Pain Processing in the Cingulate Cortex, Behavioral Studies in Humans
▶ PET and fMRI Imaging in Parietal Cortex (SI, SII, Inferior Parietal Cortex BA40)
▶ Thalamus and Visceral Pain Processing (Human Imaging)
▶ Thalamus, Clinical Pain, Human Imaging
▶ Thalamus, Clinical Visceral Pain, Human Imaging
**Functional Magnetic Resonance Imaging (fMRI)**

- Amygdala, Functional Imaging

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**Functional Restoration**

**Definition**

Functional restoration is a pain management approach geared specifically for chronic low back pain patients. This approach places a strong emphasis on function, and combines a quantitatively directed exercise progression with disability management and psychosocial interventions such as individual and group therapy.

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**Cross-References**

- Psychological Treatment of Chronic Pain, Prediction of Outcome

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**Functional Restoration Program**

- Multidisciplinary Pain Centers, Rehabilitation

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**Functional Restoration/Exercise Programs**

- Physical Conditioning Programs

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**Functioning**

- Functioning and Disability Definitions
- Physical Exercise

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**Functioning and Disability Definitions**

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**Synonyms**

Classification; Disability; Functioning; ICD; ICF

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**Definition**

Functioning; Disability; ICF; Classification; ICD

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**Introduction**

The International Classification of Functioning, Disability and Health (ICF) (WHO 2001) was intended by the WHO to be the common reference framework to describe the full spectrum of human functioning and disability. As a conceptual model and a classification system, the ICF can be applied in various ways in clinical care, health and social policy, and research, and for epidemiological and population surveys. The ICF can be used to understand health and health-related domains and compare data across regions and countries, and as a system of coding (WHO 2001). The ICF can be applied regardless of the setting, culture, and context.

As a conceptual model, the ICF illustrates the interrelationship between a health condition and its impact on the individual’s body (body functions and body structure), and activities and
participation (societal impact). This relationship may be influenced by environmental factors and personal factors (Fig. 1).

Characteristics

The current framework of functioning and disability is the ICF (WHO 2001), in which disability is determined by impairment of body structures and body functions, activity limitations, and participation restrictions. Historically, there have been two major conceptual frameworks in the field of disability: the International Classification of Impairment, Disability and Handicap (ICIDH), which is the precursor to the ICF, and the “functional limitation,” or Nagi, framework (Nagi 1964). In the ICIDH (WHO 1980), the four concepts were disease, impairment, disability, and handicap. In the Nagi framework, the four concepts were pathology, impairment, functional limitation, and disability. Different from the ICIDH, the Nagi framework was not accompanied by a classification. Building on the conceptual frameworks of the ICIDH and Nagi, the US Committee on a National Agenda for the Prevention of Disabilities developed a model emphasizing the interaction between the disabling process, quality of life, and individual risk factors (Pope and Tarlov 1991).

The ICF attempts to achieve a synthesis and integration of the different perspectives of health from biological, psychological, and social perspectives (i.e., biopsychosocial approach). It emphasizes health-related “building blocks” or domains to form specific disability models in the context of health. The ICF has addressed many of the criticisms of prior conceptual frameworks (e.g., lack of environmental consideration, purely biomedical perspective), and has been developed in a worldwide and comprehensive expert consensus process. For all these reasons, the ICF is the generally accepted conceptual framework and classification to describe a persons’ level of functioning and disability in light of his or her health condition. Disability serves as an umbrella term for impairments, activity limitations, and participation restrictions. So it can be seen as the negative term of functioning. The interaction of disability and health condition works in both directions, because the presence of disability may even modify the health condition. The level of disability may be indicated for body functions, body structures, activities and participation, and environmental by using the generic ICF qualifiers of the WHO (WHO 2001). More information on the qualifiers is provided later.

It is important to recognize that the ICF can serve as a common language (Stucki et al. 2002), in that the texts that can be created with it (ICF) can be used by different users, within their intended purpose, and their scientific orientation. The understanding of bidirectional interactions and relationships between the components of the ICF is shown in Fig. 1.

Health condition refers to any kind of disorder, illness, or disease. It may include information about pathogeneses and/or etiology. There are (possible) interactions with all or any of the components of functioning, namely, ► body functions and body structures, activities, and participation (WHO 2001).

Body functions are the physiological (and psychological) functions of body systems. ► Body structures are anatomical parts of the body. Problems in body functions and body structures are called impairments, which are defined as a significant deviation or loss (e.g., deformity) of structures (e.g., joints), and/or functions
Activity is described as the execution of a task or action by an individual. Difficulties an individual may have in executing activities are called activity limitations (e.g., limitations in mobility such as walking, climbing steps, grasping, or carrying).

Participation is described as involvement in a life situation (i.e., societal involvement). It represents the societal perspective of functioning. Problems an individual may experience in involvement in life situations are called participation restrictions. Limitations and restrictions are assessed against a generally accepted population standard. “Participation” records discordance between the observed performance and the expected performance. The expected performance is the population norm, which represents the experience of people without the specific health condition (e.g., with associated restrictions in community life, recreation, and leisure).

A person’s functioning (and disability) is conceived as a dynamic interaction between health conditions (diseases, disorders, injuries, traumas, etc.) and contextual factors. Likewise, there are (possible) interactions with all components of functioning and contextual factors.

Contextual factors are factors that constitute the context of an individual’s life, and in particular, the backgrounds against which health states are classified in the ICF. There are two sets of contextual factors: ▶Environmental factors and personal factors.

Environmental factors refer to all aspects of the external or extrinsic world that form the context of an individual’s life and, as such, may have an impact on that person’s functioning. Environmental factors include the physical world and its features, the human-made physical world, other people in different relationships and roles, attitudes and values, social systems and services, and governing policies, rules, and laws.

ICF qualifiers can be assigned to rate the problem for each domain under the ICF components on body functions, body structures, activities and participation, and environmental factors (Table 1). In the case of environmental factors, the extent of being a barrier or a facilitator is used.

Personal factors are contextual factors that relate to the individual such as age, gender, social status, life experiences, lifestyle, habits, coping styles, education, behavior, and other personal characteristics. Risk factors could be described under personal factors (e.g., lifestyle, coping mechanism) or environmental factors (e.g., living and work conditions, architectural barriers) that are associated with conditions such as pain. Bidirectional arrows in Fig. 1 indicate the possibility of forward and feedback process. Risk factors also affect the progression of disability and, may include, depending on the stage, treatment, rehabilitation, age of onset, financial resources, healthcare provision, expectations, and environmental barriers. Personal factors are defined and included in the ICF model, but not yet classified (hence, it has no categories nor qualifiers) into a coding system like the rest of the components.

The ICF is intended for use in multiple sectors that include health, education, insurance, labor, health and disability policy, etc. In the clinical
Functioning and Disability Definitions, Table 2

ICF categories of the comprehensive ICF Core Set for chronic widespread pain (brief core set marked with *)

<table>
<thead>
<tr>
<th>ICF category (code)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body functions</strong></td>
<td></td>
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<tr>
<td>b122</td>
<td>Global psychosocial functions</td>
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<tr>
<td>b126</td>
<td>Temperament and personality functions</td>
</tr>
<tr>
<td>b130*</td>
<td>Energy and drive functions</td>
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<tr>
<td>b134*</td>
<td>Sleep functions</td>
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<tr>
<td><strong>Specific mental functions</strong></td>
<td></td>
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<tr>
<td>b140</td>
<td>Attention functions</td>
</tr>
<tr>
<td>b147*</td>
<td>Psychomotor functions</td>
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<tr>
<td>b152*</td>
<td>Emotional functions</td>
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<tr>
<td>b160*</td>
<td>Content of thought</td>
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<tr>
<td>b164</td>
<td>Higher-level cognitive functions</td>
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<tr>
<td>b180</td>
<td>Experience of self and time function</td>
</tr>
<tr>
<td><strong>Additional sensory functions</strong></td>
<td></td>
</tr>
<tr>
<td>b260</td>
<td>Proprioceptive function</td>
</tr>
<tr>
<td>b265</td>
<td>Touch function</td>
</tr>
<tr>
<td>b270</td>
<td>Sensory function related to temperature and other stimuli</td>
</tr>
<tr>
<td>b280*</td>
<td>Sensation of pain</td>
</tr>
<tr>
<td><strong>Functions of the haematological and immunological systems</strong></td>
<td></td>
</tr>
<tr>
<td>b430</td>
<td>Haematological system functions</td>
</tr>
<tr>
<td><strong>Additional functions and sensations of the cardiovascular and respiratory systems</strong></td>
<td></td>
</tr>
<tr>
<td>b455*</td>
<td>Exercise tolerance functions</td>
</tr>
<tr>
<td><strong>Genital and reproductive functions</strong></td>
<td></td>
</tr>
<tr>
<td>b640</td>
<td>Sexual functions</td>
</tr>
<tr>
<td><strong>Functions of the joints and bones</strong></td>
<td></td>
</tr>
<tr>
<td>b710</td>
<td>Mobility of joint functions</td>
</tr>
<tr>
<td><strong>Muscle functions</strong></td>
<td></td>
</tr>
<tr>
<td>b730*</td>
<td>Muscle power functions</td>
</tr>
<tr>
<td>b735</td>
<td>Muscle tone functions</td>
</tr>
<tr>
<td>b740</td>
<td>Muscle endurance functions</td>
</tr>
<tr>
<td><strong>Movement functions</strong></td>
<td></td>
</tr>
<tr>
<td>b760*</td>
<td>Control of voluntary movement functions</td>
</tr>
<tr>
<td>b780</td>
<td>Sensations related to muscles and movement functions</td>
</tr>
<tr>
<td><strong>Body structures</strong></td>
<td></td>
</tr>
<tr>
<td>s770</td>
<td>Additional musculoskeletal structures related to movement</td>
</tr>
<tr>
<td><strong>Activities and participation</strong></td>
<td></td>
</tr>
<tr>
<td>Applying knowledge</td>
<td></td>
</tr>
<tr>
<td>d160</td>
<td>Focusing attention</td>
</tr>
<tr>
<td>d175*</td>
<td>Solving problems</td>
</tr>
</tbody>
</table>

Functioning and Disability Definitions, Table 2 (continued)

<table>
<thead>
<tr>
<th>ICF category (code)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General tasks and demands</strong></td>
<td></td>
</tr>
<tr>
<td>d220</td>
<td>Undertaking multiple tasks</td>
</tr>
<tr>
<td>d230*</td>
<td>Carrying out daily routine</td>
</tr>
<tr>
<td>d240*</td>
<td>Handling stress and other psychological demands</td>
</tr>
<tr>
<td><strong>Changing and maintaining body position</strong></td>
<td></td>
</tr>
<tr>
<td>d410</td>
<td>Changing basic body position</td>
</tr>
<tr>
<td>d415</td>
<td>Maintaining a body position</td>
</tr>
<tr>
<td><strong>Carrying, moving, and handling objects</strong></td>
<td></td>
</tr>
<tr>
<td>d430*</td>
<td>Lifting and carrying objects</td>
</tr>
<tr>
<td><strong>Walking and moving</strong></td>
<td></td>
</tr>
<tr>
<td>d450*</td>
<td>Walking</td>
</tr>
<tr>
<td>d455</td>
<td>Moving around</td>
</tr>
<tr>
<td><strong>Moving around using transportation</strong></td>
<td></td>
</tr>
<tr>
<td>d470</td>
<td>Using transportation</td>
</tr>
<tr>
<td>d475</td>
<td>Driving</td>
</tr>
<tr>
<td><strong>Self-care</strong></td>
<td></td>
</tr>
<tr>
<td>d510</td>
<td>Washing oneself</td>
</tr>
<tr>
<td>d540</td>
<td>Dressing</td>
</tr>
<tr>
<td>d570</td>
<td>Looking after one’s health</td>
</tr>
<tr>
<td><strong>Acquisition of necessities</strong></td>
<td></td>
</tr>
<tr>
<td>d620</td>
<td>Acquisition of goods and services</td>
</tr>
<tr>
<td><strong>Household tasks</strong></td>
<td></td>
</tr>
<tr>
<td>d640*</td>
<td>Doing housework</td>
</tr>
<tr>
<td><strong>Caring for household objects and assisting others</strong></td>
<td></td>
</tr>
<tr>
<td>d650</td>
<td>Caring for household objects</td>
</tr>
<tr>
<td>d660</td>
<td>Assisting others</td>
</tr>
<tr>
<td><strong>General interpersonal interactions</strong></td>
<td></td>
</tr>
<tr>
<td>d720</td>
<td>Complex interpersonal interactions</td>
</tr>
<tr>
<td><strong>Particular interpersonal interactions</strong></td>
<td></td>
</tr>
<tr>
<td>d760*</td>
<td>Family relationships</td>
</tr>
<tr>
<td>d770*</td>
<td>Intimate relationships</td>
</tr>
<tr>
<td><strong>Work and employment</strong></td>
<td></td>
</tr>
<tr>
<td>d845</td>
<td>Acquiring, keeping and terminating a job</td>
</tr>
<tr>
<td>d850*</td>
<td>Remunerative employment</td>
</tr>
<tr>
<td>d855</td>
<td>Non-remunerative employment</td>
</tr>
<tr>
<td><strong>Community, social and civic life</strong></td>
<td></td>
</tr>
<tr>
<td>d910</td>
<td>Community life</td>
</tr>
<tr>
<td>d920*</td>
<td>Recreation and leisure</td>
</tr>
<tr>
<td><strong>Environmental factors</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Products and technology</strong></td>
<td></td>
</tr>
<tr>
<td>e1101*</td>
<td>Drugs</td>
</tr>
</tbody>
</table>

(continued)
context, it is intended for use in needs assessment and matching interventions to specific health states, rehabilitation program, and outcome evaluation. The joint use of the ICF and the International Classification of Diseases (ICD) needs to be addressed when applying the ICF in medicine in general (Kostanjsek et al. 2011a, b) and in rehabilitation (Kostanjsek et al. 2011b) and pain rehabilitation in particular. The WHO considers the ICF and the ICD to be distinct but complementary classifications. According to this view, patient functioning and health are associated with a condition or disease, but are not merely and necessarily a consequence of it. However, with the hundreds of codes within the ICF, the ICF needs to be tailored in order to be practical. Hence, for practical purposes, short lists of ICF categories called ICF Core Sets have been developed (www.icf-research-branch.org/home.html) and are relevant to a number of health conditions with a high burden, including chronic widespread pain, i.e., pain in several regions of the body (Cieza et al. 2004a). ICF Core Sets have also been developed for several other conditions that may have pain as a common denominator, including low back pain (Cieza et al. 2004b), ankylosing spondylitis (Boonen et al. 2010), osteoarthritis (Dreinhofer et al. 2004), and rheumatoid arthritis (Stucki et al. 2004). Table 2 shows the ICF Core Set for chronic widespread pain (Cieza et al. 2004a). A comprehensive version of the ICF Core Set includes the ICF categories (units of domains) considered relevant for a comprehensive multidisciplinary assessment such as inpatient settings. The brief version of an ICF Core Set, marked with an asterisk (*) in the table, includes those ICF categories to be assessed in every clinical study and clinical encounter to allow for a meaningful description of a patient’s functioning and health. A practical demonstration of how to use the ICF is shown in Fig. 2.

### Current Measures in Pain Can Be Linked to the ICF

There are measures available, generic or condition specific, that can be linked to the ICF according to the domains that these measures cover. The concepts contained in such measures can be linked to the ICF using defined linkage rules (Cieza et al. 2005). For example, low back pain can be linked to the body function domain of the ICF, and other measures that assess pain and depression in relation to activities of daily living can be linked to the activities and participation domains of the ICF. The linking can be made more specific to the category level (e.g., b280 for sensation of pain).

It is important to recognize that different measures address different components of the ICF, and it seems that the concepts contained in these measures are generally represented in the ICF (Weigl et al. 2003). Condition-specific measures typically focus on body functions and activities, while generic measures tend to cover activities and participation including aspects of physical, mental, and social health. Contextual factors are hardly covered by any of these instruments.

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**Functioning and Disability Definitions, Table 2 (continued)**

<table>
<thead>
<tr>
<th>ICF category (code)</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Support and relationships</td>
<td></td>
</tr>
<tr>
<td>e310*</td>
<td>Immediate family</td>
</tr>
<tr>
<td>e325</td>
<td>Acquaintances, peers, colleagues, neighbors, and community members</td>
</tr>
<tr>
<td>e355*</td>
<td>Health professionals</td>
</tr>
<tr>
<td>Attitudes</td>
<td></td>
</tr>
<tr>
<td>e410*</td>
<td>Individual attitudes of immediate family members</td>
</tr>
<tr>
<td>e420</td>
<td>Individual attitudes of friends</td>
</tr>
<tr>
<td>e425</td>
<td>Individual attitudes of acquaintances, peers, colleagues, neighbors, and community members</td>
</tr>
<tr>
<td>e430</td>
<td>Individual attitudes of people in positions of authority</td>
</tr>
<tr>
<td>e450</td>
<td>Individual attitudes of health professionals</td>
</tr>
<tr>
<td>e455</td>
<td>Attitudes of other professionals</td>
</tr>
<tr>
<td>e460</td>
<td>Societal attitudes</td>
</tr>
<tr>
<td>e465</td>
<td>Social norms, practices, and ideologies</td>
</tr>
<tr>
<td>Services, systems, and policies</td>
<td></td>
</tr>
<tr>
<td>e570*</td>
<td>Social security services, systems, and policies</td>
</tr>
<tr>
<td>e575</td>
<td>General social support services, systems, and policies</td>
</tr>
<tr>
<td>e580</td>
<td>Health services, systems, and policies</td>
</tr>
<tr>
<td>e590</td>
<td>Labor and employment services, systems, and policies</td>
</tr>
</tbody>
</table>
Nonetheless, there is a need to address all components when assessing functioning and health in patients with chronic health conditions (Ewert et al. 2004).

Finally, it is important to note that the perspective of functioning, disability, and health is different when viewed from a medical versus functioning-oriented perspective, e.g., in rehabilitation. From the medical perspective, functioning and health are seen primarily as a consequence of a disease or condition. Accordingly, medical interventions are targeted toward mitigation or elimination of the disease process. From a broader view, the measurement of functioning, disability, and health is required to evaluate patient-relevant outcomes of an intervention. Hence, from a functioning-oriented or rehabilitation perspective as depicted in the ICF, patients’ functioning and health are associated with, but not merely a consequence of, a condition or disease. Furthermore, functioning and health are not only seen in association with a condition, but also in association with personal and environmental factors. Therefore, the measurement of functioning, disability, and health is relevant to evaluate intervention outcomes and for the diagnosis (assessment) and overall clinical care. For the management of patients with pain conditions, consideration of the individual’s functioning is becoming more and more critical than before.

**Summary**

In summary, the ICF can be used as a conceptual framework and classification system to examine and understand the impact and relation of pain
with regard to the functioning and disability of an individual. The ICF provides a holistic biopsychosocial perspective that is beyond the traditional biomedical model and, hence, can aid in the thought process to guide clinical decision making and clinical care in the context of pain and pain-related conditions.

Acknowledgment Previous edition of this entry was written by Gerold Stucki and Thomas Ewert.

References


Funiculus

**Definition**

Longitudinal subdivisions of the spinal white matter that are named according to their location within the spinal cord.

**Cross-References**

▶ Spinothalamic Projections in Rat