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Alloknesis and hyperknesis - mechanisms, assessment methodology and clinical implications of itch sensitization

Running head: *Mechanical itch dysesthesias*

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1. Introduction

Chronic itch is a prominent symptom of numerous skin diseases, in addition to certain neuropathic and systemic conditions [135]. Common conditions presenting with itch include atopic dermatitis (AD), psoriasis, post-herpetic neuralgia, kidney failure, and liver diseases [34,148,158,159]. Similar to chronic pain, chronic itch often presents with additional somatosensory abnormalities [10,34,65,109]. As such, patients with chronic itch are often bothered by mechanical itch dysesthesias, warmth-evoked itch exacerbations, pain, stinging, pricking and/or burning skin sensations [10,34,45,68,140,161]. Itch dysesthesias refer to dysfunctional sensory states, in which considerable itch is evoked by light tactile stimuli (e.g. from clothing or touch), or by stimuli which would normally induce only mild itching or pain [10,21,65,124] (Fig. 1A and B).

As early as 1938 Bickford described that immediately surrounding an itch provocation (such as a histamine skin puncture), an area where innocuous mechanical stimulation produces itch developed. He termed this phenomenon "itchy skin" [31]. The alternate, more precise term "alloknesis" was later coined by LaMotte *et al*. in 1988 when revisiting and extending on Bickford's findings [31,79,81]. Moreover, the term "hyperknesis" was proposed to act as an umbrella term also encompassing the state in which there is enhanced itch to normally itch-provoking stimuli or lowered itch threshold to a given stimulus [36,79,81,131] (comparable to *hyperalgesia* for pain [64]). These dysesthetic states may last for a couple of minutes to hours after an itch provocation or can be a persistent feature, as seen in patients with chronic itch due to AD [10,63,65]. Itch-associated dysesthesias such as mechanical alloknesis and hyperknesis, are noticeably analogue to the dysesthesias found in various experimental and clinical pain conditions [68,124,134]. For instance, while patients with painful peripheral neuropathy may report pain in response to light innocuous brush strokes applied to the skin in or around painful areas (*allodynia*), patients with chronic itch conditions frequently find such stimuli to be itchy (*alloknesis*) [8,63,124].

Such somatosensory reactivity patterns are caused by neuronal sensitization, and those signs associated with pain (allodynia and hyperalgesia) have been elaborately studied both mechanistically [123,151], and in diverse clinical cohorts (covered in detail elsewhere [19,24,37,86,119]). Therefore, much of the present methodological, phenomenological and mechanistic evidence on mechanical allo- and hyperknesis stems from obvious parallels related to pain-associated dysesthesias as well as from preclinical and human experimental models of itch [8,21,79,81,124,130,132]. Notably, the neurophysiology of itch transmission is highly entwined with the nociceptive system, with no clear differentiating features at the peripheral level. This has given rise to different hypotheses explaining how pruriceptive and nociceptive information coming from the same primary afferents is decoded in the CNS (see review on the subject [82]).

In pain research, highly standardized quantitative sensory testing (QST) methodology [20,55,92,156] and diverse human models of sensitization has spawned the notion of potential *sensory phenotyping* for diagnostic, prognostic and therapeutic purposes [18,22,24]. The assessment of alloknesis and hyperknesis allow for surrogate measures of neuronal sensitization in itch patients. However, itch-specific QST protocols are much less advanced and studied compared to pain. It remains to be explored whether assessment of itch sensitization correlates is useful for the purpose of subgrouping, for instance in patients with AD, akin to the sensory phenotyping being utilized within pain research [24,46,139,157]. The purpose of this review is to provide an overview of the definitions, present evidence regarding assessment techniques, and mechanisms of mechanical allo- and hyperknesis, while linking this evidence to the more familiar concepts of allodynia and hyperalgesia.

2. Definitions and terminology

Allodynia and hyperalgesia (the pain-related equivalents to alloknesis and hyperknesis) have been defined and redefined on several occasions [64,89,95–97,123]. The present review adheres to the IASP taxonomy task force definitions of 2008 (elaborately described by, e.g., Loeser and Treede [89,138], and Sandkuhler [123]). These definitions are not in full agreement with the current IASP definitions (the updated version of the 1994 taxonomy[64]).

Hyperalgesia ("increased pain sensitivity") is characterized as an umbrella term describing all types of increased pain sensitivity while the term; allodynia ("pain in response to a non-nociceptive stimulus") is restricted to scenarios where the nature of the evoking stimulus is such that it is deemed unable to activate nociceptive primary afferents [96,123,138]. This review uses a similar definitional principle for allo- and hyperknesis, i.e. using hyperknesis whenever there is doubt as to the prompting stimulus' capability of activating pruriceptive afferent (See Fig. 1A and B). This is also generally in accordance with the original definitions [79,81].

In the literature conflicting nomenclature is currently being used to describe allo- and hyperknesis phenomena. Some studies describe alloknesis solely as itch occurring in response to innocuous (dynamic) tactile stimuli, and hyperknesis only as itch in response to punctate pricking stimuli, which may or may not be considered mildly painful under normal conditions [63,111] (see Table 1). Other studies denote alloknesis as itch in response to punctate von Frey stimuli, e.g. up to 70 mN force [1,33,107] (i.e. far above the threshold for activating mechano-sensitive C-nociceptors). Other reports describe assessments of 'mechanical itch sensitivity', using von Frey filaments in chronic itch patients or after acute itch provocations, omitting the terms alloknesis or hyperknesis [13,75,77,78]. Discrepancies exist regarding the extent to which these stimuli are reported to produce itch under normal conditions, and sometimes this is not assessed. It has also been noted that hyperknesis could simply refer to an exaggerated response to chemical stimuli, such as increased itch following histamine, as have been observed in lesional AD skin [54,67,79], but this usage has never caught on. The definitions applied in the present review prevent that a unitary occurrence, such as increased itch sensitivity to punctate mechanical stimuli or chemical itch provocations, as being classifiable as both alloknesis and hyperknesis at the same time, depending on how it is tested (threshold vs. suprathreshold assessments).

Recently, 'alloknesis' has been used to characterize itch and itch aggravation in response to noxious heat and innocuous warmth stimuli [38,102]. Future research might clarify whether gentle warming-induced itch is indeed a type of alloknesis [102] or whether it is an itch-related analogue to inflammatory hyperalgesia. The particular modality-switch dysesthesia in which itch is evoked in by algogens [63] or exclusively painful

stimuli, is not includable in current definitions of alloknesis and hyperknesis (See Table 1). It has been observed in patients with AD, in healthy subjects with evoked contact dermatitis and in mice models [5,38,102] and is not associated with any specific term. In this review the term *algoknesis* will be applied to describe this sensory phenomenon, which conceivably rely on mechanisms distinct from those of hyperknesis and alloknesis. Itch in response to noxious heat, e.g. observed in AD patients will accordingly be characterized as 'heat algoknesis'.

3. Mechanisms of alloknesis and hyperknesis

Given the similarities between itch and pain-evoked dysesthesias, it is natural that aspects of the proposed underlying mechanisms are based on similar experimental approaches and inferences [68,80,124]. Alloknesis and hyperknesis typically occur within the region of an itch provocation, and in the skin immediately surrounding the provocation site. Consequently, the dysesthesias are referred to as being *primary* and *secondary*, respectively. Mechanistically, two potentially overlapping sensitization processes exist; sensitization of spinal neurons (central sensitization) and sensitization of the peripheral neurons (peripheral sensitization). In a state of central itch sensitization, pruriceptive spinothalamic tract (STT) neurons respond more vigorously to normal input from pruriceptive primary neurons and afferent mechanosensitive signaling, normally associated with light touch (alloknesis) or mild pain/itch (hyperknesis) converges onto the STT neurons (Fig. 2A and B for models) [82,123]. The corresponding pain phenomena (i.e. secondary allodynia and hyperalgesia) also rely on sensitization of STT neurons [132]. These pain dysesthesias do not cross the midline [83] or extend beyond a narrow anesthetized strip of skin [72], are reduced or abolished by myelinated fiber blocks [73,90,163] and are mostly unaffected by ablation of capsaicin-sensitive nociceptors [57,90,163]. This all indicates that secondary allodynia and hyperalgesia are segmentally restricted, heterosynaptic, spinal sensitization phenomena which rely on initial intact input from mechano-sensitive, $TRPV^-$ fibers. However, in prolonged inflammatory/neuropathic pain and itch states, additional or entirely different mechanisms potentially relying more on peripheral sensitization, disinhibition and supraspinal changes, may also be involved [22,84,123]. Strong indirect evidence on the close link between itch and pain-evoked dysesthesias comes from experimental human psychophysical studies. When a conditioning painful stimulation such as an intra-dermal capsaicin injection [36], or painful transcutaneous electrical stimulation [106,107] is pre-applied to a skin area it will exhibit decreased itch sensitivity and inhibited itch dysesthesia development long after the spontaneous pain resolves. This may in part be due to the fact that the same neuronal substrates are recruited in the sensitization processes, e.g., low-threshold mechano-receptor (LTM) input to sensitized STT nociceptive and pruriceptive projection neurons are likely responsible for allodynia and alloknesis, respectively. Remarkably, in patients with

chronic itch associated with AD, substantial itch and pain can co-exist in lesional skin [10,140] and the same is true for robust mechanical hyperalgesia and hyperknesis [10].

3.1 Alloknesis: In non-human primates, injection of histamine results in a small number of pruriceptive STT neurons exhibiting increased responses to stroking (alloknesis), or to a punctate skin stimulus (hyperknesis), evoking mild pricking pain sometimes followed by itch in humans [43,129]. As outlined above, itch evoked by brush strokes represents a central sensitization phenomenon of wide dynamic range STT neurons resulting from an initial PmC or C-mechano-insensitive (CMi)-mediated pruriceptive barrage (see Fig. 2A and Table 1). This is circumstantially supported by the fact that the primary afferent substrate for light touch is LTMs (Aβ- and C-tactile fibers) and that this type of stimulation rarely results in itch under normal conditions. In this context, it is important to note that in trigeminally innervated areas very low intensity mechanical stimuli (such as those used to assess alloknesis or minute vibration of a vellus hair), are sufficient to produce an itch or tickle sensation [11,49]. Remarkably, the same trigeminal skin areas exhibits decreased sensitivity to common chemical itch provocations [11,49,91]. A recent rodent study quantifying alloknesis by low intensity von Frey filaments suggested that mechanically evoked itch might be mediated by LTMs, and showed that such itch is constantly gated by a subpopulation of inhibitory neuropeptide Y^+ interneurons under normal conditions [33]. Experiments on allodynia in non-human primates show that capsaicin-induced mechanical allodynia occurs in the absence of increased sensitivity of the nociceptive primary afferents [27], while STT neurons exhibited enhanced responsiveness to normal input [132]; thus strongly suggesting central sensitization and subsequent increased convergence to be the driving mechanism. It has recently been shown that not only the STT but also the spinoparabrachial pathway is involved in ascending itch transmission [101]. It remains unknown whether these projection neurons are also involved in mediation of itch sensitization. A large proportion of neurons in both the STT and spinoparabrachial pathway express the neurokinin-1 receptor [137]. When these neurons are selectively ablated robust inhibition of alloknesis is observed AD mice [6], thus potentially implicating both ascending pathways.

Notably, areas of alloknesis (and allodynia) rapidly retract when cooling the site of spontaneous itch/pain indicating that at least weak constant pruriceptive C-nociceptor input is required [111,131]. This observation aligns with evidence from chronic itch patients where alloknesis is restricted to lesional and peri-lesional skin [63]. Pharmacological modulation studies in mice and humans show that the μ-antagonist naltrexone inhibits itch and the development of alloknesis [1,58,116], while systemic μ-agonist analgesics generally induce or aggravates itch and exhibits anti-allodynic effects [30,74,125]. The exact spinal circuitry that mediates secondary alloknesis, hyperknesis as well as secondary pain dysesthesias remains to be fully explored. See Peirs *et al*. 2016 for a review of recent advances [112].

3.2 Hyperknesis: The mechanisms of hyperknesis are less clear, and it remains unknown which type of afferents mediate the mild itch resulting from punctate stimuli [49,66]. Hyperknesis is possibly mediated by type-I Aδ-fibers through a central mechanism when occurring secondarily to an itch provocation or an actively itchy skin lesion, as is the case for secondary pinprick hyperalgesia (Fig. 2B). On the other hand, itch evoked by pricking stimuli occurs with a 0.5-2 second delay [13,65], indicating PmC-fibers as the peripheral sensor (Table 1). When pinprick hyperknesis occurs within an active skin lesion or an area pretreated with an itch provocation, additional peripheral contribution is possible [10,63,65]. In the case of an inflammatory perturbation, mechanically insensitive afferents can develop *de novo* mechanosensitivity and mechano-nociceptors respond more vigorously to suprathreshold stimuli [17,98,117]. In chronically itchy AD lesions (and to a lesser extend beyond the lesions) profound pinprick-evoked hyperknesis occurs, suggesting concomitant peripheral and central sensitization contributions [10,65,75]. A sub-population of nociceptors potentially responsible for punctate mechanically evoked itch are the non-peptidergic mas-related G-coupled protein receptor D (MrgprD)-expressing C-fibers. These terminate very superficially in the epidermis [164], are implicated in non-histaminergic itch [87], have low mechanical thresholds [152], and are sensitized to punctate stimuli in a mouse model of contact dermatitis [117]. The same contact dermatitis model also produces robust pinprick hyperknesis in humans [111]. In AD, intra- and extra-lesional itch sensitization to chemical provocations (algogens [63] and pruritogens [10,56,67,75,136]), is mechanistically unaccounted for, possibly reflecting protracted cutaneous aberrations. A study has suggested altered transducer expression, e.g. increased proteinase-activated receptor-2 (PAR2) on afferent nerve fibers in lesional AD skin [136]. It is unlikely that current acute human models of itch sensitization mimic the sensory aberrations associated with prolonged or chronic inflammatory lesional and related skin alterations [8,65]. Notably, inflammatory heat hyperalgesia is overwhelmingly driven by peripheral sensitization [98], but this is rather different from the sensory abnormalities found in lesional AD skin [65], where normally painful heat stimuli evoke itch, and innocuous warming of the skin often exacerbates ongoing itch [10]. The latter observation has been successfully reproduced in rodent itch models and is thought to predominantly occur following provocations with specific pruritogens such as serotonin [53,102]. Human surrogate models known to induce sub-acute peripheral pain sensitization, such as UVB-damage (inflammatory) and intra-dermal NGF (non-inflammatory), both induce mild primary pinprick hyperknesis at baseline but have limited impacton chemical itch provocations [16]. The well-studied mechanical hyperalgesia of these models differs from that of intradermal capsaicin, as it is driven by peripheral sensitization and associated with no/limited spontaneous pain. According to one study, the NGF model do evoke increased sensitivity to cowhage occurring simultaneously with the maximal mechanical hyperalgesia, indicative of sensitization of PmC-fibers [71,121].

A complicating factor in term of understanding hyperknesis, is that the manner in which itch and pain are differentially encoded (allowing PmC-nociceptors to be both pruriceptive and nociceptive), remains unknown. If the proposed notion of *spatial contrast* is indeed a crucial encoding component for discrimination between itch and pain [103,104], then the mechanism for hyperknesis in lesional skin of patients with itch could simply be either be highly scattered loss of PmC-fibers (as indicated by nerve morphology studies in chronic itch patients [114]), or sensitization of a small subset of PmC-fibers. Both of these scenarios would likely increase itch in response to pinprick stimuli by giving rise to signaling with unusually high spatial contrast.

4. Quantitative assessment of mechanical alloknesis and hyperknesis

4.1 Animal studies: Alloknesis is assessed by eliciting scratching in response to low intensity mechanical stimuli that would not normally elicit scratching for instance in C57BL/6 mice (Table 2) [1]. After intradermal injection of certain pruritogens into the rostral back, a very weak von Frey filament (0.7 mN) is applied to the skin area around the injection site. The presence or absence of an evoked hind limb scratch bout directed toward a site of innocuous touch is noted. Touch-evoked scratching is usually observed less than a second after the stimulus. Pharmacological validation of this assessment method has been done by showing effective abolishment of alloknesis after treatment with opioid antagonists, selective κ-opioid-agonists and H1 histamine antagonists (when the chemical itch provocation is histamine-dependent) [1,2,58]. The onset of alloknesis is often delayed relative to the onset of chemically evoked scratching, implying that substantial constant itch input is required to develop alloknesis. Touch-evoked scratching after innocuous stimuli is also present in experimental mouse models of chronic itch (Table 2). In humans alloknesis is often assessed by brush strokes (*section 4.2*) and although brush-evoked scratching has not yet been reported in rodents, pruriceptive signaling in response to brush stimuli is enhanced following an intrathecal injection of morphine in rat pruriceptive trigeminothalamic tract neurons [100].

Mechanical hyperknesis has not been clearly established in rodents, due to the lack of a standardized method to assess a mechanical itch threshold in naive rodents. Mechanically evoked itch in response to graded stimulation, peaks below the force of the mechanical pain threshold in humans (as well as the minimum force normally required to activate PmC-nociceptors) [11,65]. Additionally, the relationship between mechanical force and evoked itch intensity follows an inverted U-shaped curve. One study reported that few scratch bouts were elicited by application of graded von Frey filaments in naive mice [33], but even with the most effectively itch evoking von Frey filament force (0.7 mN) scratch bouts were only

elicited in response to less than 15% of the stimuli. A fundamental difference regarding the quantification of itch is that animal readouts are always scratch-dependent. Oppositely, humans can easily rate an evoked itch sensation, which is so mild that it would rarely elicit an actual scratch. In human studies this is almost always the case for the mechanically evoked itch in healthy skin [9,65,77]. Lastly, as there are rodent strain differences in mechanical sensitivity [99], the mechanical itch thresholds should be assessed in each strain tested. Outbred mouse strains might not be suitable for pre-clinical studies of mechanical itch due to their genetic heterogeneity.

4.2 Human experimental studies: Using human surrogate models of acute and sub-acute itch, detailed assessments of allo- and hyperknesis to mechanical stimuli can be undertaken (Table 2). Intradermal injection, a skin prick, or iontophoretic delivery of a pruritogen such as histamine, mucunain, or serotonin evokes acute itch lasting 5-20 minutes [8,62,131]. During, or as the itch subsides, the *spatial* extent of alloknesis and hyperknesis can be assessed by stimulating the skin surrounding the injection site [66,111,131,149]. Alloknesis is commonly assessed using a light brush, while hyperknesis is often assessed with a pinprick stimulator or von Frey monofilaments [66,111]. Typically, stimuli are delivered in small increments (0.5-2 cm) following multiple vectors moving from well away from the injection site and towards it. The subjects are asked to notify the investigator when the stimuli turn from producing pure innocuous tactile sensations into itch (alloknesis) or from a pricking/slightly itchy to evoking noticeably more itch (hyperknesis) [131]. This procedure can be repeated in short succession (as areas of alloknesis and hyperknesis are dynamic) to decrease variability and produce an accurate spatial mapping of the extent of allo- or hyperknesis. The drawbacks are that it is: 1) time consuming; 2) vulnerable to false positives (a control is always required); and 3) relies on a localized initial itch provocation (making it difficult to apply to endogenously evoked itch in patients). Alternatively, the *intensity* of the allo- and/or hyperknesis can be assessed in the immediate vicinity of an itch provocation [11,63,75,111]. Here, the stimulation is conducted several times, with multiple intensities close to the itch provocation site, but usually not immediately on the bleb or wheal. The subject is asked to rate the presence and/or the intensity of the mechanically evoked itch [10,63,67]. The intensity, or simply the presence of alloknesis, can be quantified in response to brush strokes or cotton wool stimuli and the intensity of hyperknesis in response to von Frey or pin prick stimuli [11,63]. Evidence suggests that punctate stimuli around or immediately below the pinprick pain threshold are most effective, and do also occasionally produce mild itch in unaffected skin. This method is faster than the area approach but does not detect the spatial outline of the assessed dysesthesias and relies on the subject providing a magnitude rating rather than simply a shift in perception. On the other hand, the method lends itself more readily to be used, e.g. on lesional, peri-lesional, or non-lesional skin in patients [10,65,75,78]. Both methods can be used to assess different itch

provocations or interventions as well as to assess the temporal development of itch dysesthesias. These methods are entirely paralleled by the techniques used in pain research [120,130], where experimentally provoked allodynia and hyperalgesia have been extensively studied. In pain research, these methods have been used for instance in an attempt to measure objective correlates of central sensitization [35], or to characterize the peripheral nociceptors involved in induction of long-term potentiation-like pain facilitation [57].

4.3 Clinical studies: Several studies have performed explorative assessments of allo- and hyperknesis in patients with chronic itch in both lesional and non-lesional skin areas as well as before and after experimental itch elicitation (Table 3). Generally, one of two methods have been applied in previous studies: 1) alloknesis or hyperknesis have been assessed in lesional and/or non-lesional skin of patients using an intensity approach, i.e. patients and healthy controls are requested to rate if, and how much itch they perceive in response to selected mechanical stimuli (brush, wool fibers or pinprick) [10,65,75]; 2) patients and controls receive an itch provocation, e.g., histamine or electrically induced itch, in non-lesional skin (homologous areas for controls) and subsequently the area of allo- or hyperknesis is mapped as described in *Section 4.2* [66,147,149]. A few studies have used the spatial extent method outlined above only after an experimental itch induction has been conducted [147,149], excluding the detection of potential baseline differences between chronic itch patients compared to healthy controls [63]. Both chronic itch and pain may lead to generalized somatosensory changes and thus even seemingly unaffected areas are not necessarily suitable control areas [52,75,77]. For instance, increased hyperknesis, increased mechanical pain sensitivity and facilitated itch responses to cowhage provocations were recently observed in non-lesional skin in patients with AD, compared to homologous skin areas in matched controls [10]. Particularly when stimulations are performed in patients with inflammatory skin disorders, barrier alterations must be considered as potential as biasing factors completely unrelated to cutaneous neuronal sensitivity. For instance, pinprick perception might be altered in lichenified skin [10], responses to chemical provocations delivered by iontophoresis might be exaggerated in excoriated areas with reduced barrier integrity, and the temporal profile of evoked itch might be affected by increased or reduced vasomotor reactions to pruritogens by affecting local tissue clearance [11,67].

5. The applicability of itch dysesthesia assessments

5.1 Mechanical itch dysesthesias in patients: Despite diverse assessment methodology clinical studies of alloknesis and hyperknesis demonstrate a relatively consistent pattern of results (Table 3). Most studies

have been performed in patients with chronic itch due to AD. When quantifying the spatial extent of alloknesis or hyperknesis following an itch provocation in non-lesional skin, AD patients do not develop larger areas of mechanical dysesthesias than healthy controls [59,66,147,149]. However, it is evident that when using the intensity quantification approach both robust alloknesis and hyperknesis occur in lesional AD skin [10,63,65,75], whereas good evidence is lacking from other chronic itch conditions. Results from studies applying the intensity quantification approach without prior itch provocation in non-lesional skin of patients with AD are more inconsistent. A single study assessing alloknesis found no evidence of it occurring in non-lesional AD skin [63]. Alloknesis has previously been described in case-studies of neuropathic itch patients as occurring peri-focally, restricted to areas of moderate to severe itch [7,15], and is likely more or less dependent on ongoing spontaneous itch nearby [111,131]. With regards to hyperknesis in AD, Ikoma *et al*. 2004, documented significant lesional and peri-lesional hyperknesis in response to weighted needle stimulation, while Laarhoven *et al*. 2007 and Andersen *et al*. 2017 observed significant hyperknesis in both lesional and non-lesional skin probed using von Frey stimulators (see Table 3). Significant inter-variability in the severity of hyperknesis seems evident amongst patients with AD, possibly indicating the existence of patient subgroups with high vs. low mechanical itch sensitization (Fig. 3A and B) [10]. Extra-lesional hyperknesis appears to almost exclusively occur in patients also displaying hyperknesis in lesional skin (Fig. 3C and D) [10]. In painful peripheral neuropathy a well-characterized sensory sub-phenotype is characterized by prominent mechanical hyperalgesia, e.g., to pinprick stimuli [24]. This particular subgroup is proposed to have increased analgesic responses to sodium-channel blockers and gabapentinoids [24,47].

5.2 Disinhibition as a cause of itch sensitization: Itch, akin to pain, is under both segmental and supraspinal descending inhibitory control [26,94]. The former is clearly evident from the itch relieve obtainable by homotopic or perilesional counter-stimuli such as scratching or heat [14,160], while the latter has been shown using conditioned itch modulation paradigms in patients and healthy controls [76] (an approach adapted from psychophysical pain research[108,154]). It is unclear whether blunted responsiveness in either of these endogenous inhibitory systems contributes to itch dysesthesias in chronic itch patients. However, indications of both reduced segmental inhibition [69,127] (Fig. 2C), and impaired descending itch inhibition have been reported [76]. Such assessments have been performed with mostly non-validated psychophysical methodology. A recent experimental study in healthy human volunteers indicates that pain-evoked recruitment of descending inhibitory signaling diminishes not only itch but also the development of hyperknesis following electrically induced itch [12]. This is in line with evidence from the pain field showing that conditioned pain stimulation reduces the intensity of secondary brush-evoked allodynia [150] following intradermal injection of capsaicin. Given the severity of partially self-inflicted

lesions and cutaneous pain co-existing with itch in AD [10,34,109,140], it is not unreasonable to suspect blunted pain-evoked inhibition in this condition as a previous implied [65,69]. This is likely caused by spinal disinhibition of itch; e.g., peripheral antinociceptive endogenous opioid expression is decreased in inflammatory itch conditions and as pain thresholds are usually normal [10]. Validated psychophysical assessment methods are needed before it can be established whether dysfunctional segmental or supraspinal descending itch inhibition is a feature in chronic itch conditions. Reduced descending pain inhibition measured by conditioned pain modulation (CPM) paradigms, has been found in numerous chronic pain conditions and is implicated in the pain progression [52,110,154,155]. Notably, the effect of drugs enhancing endogenous pain inhibition, such as duloxetine, can be predicted by CPM, in that low CPM-responses correlate with increased analgesia [157].

5.3 Itch sensitization to non-mechanical provocation modalities: In rodents, innocuous warming aggravates serotonergic but not histaminergic itch [5]. AD patients consistently report that their itch is worsened by warmth [10,51,142]. However, in acute human models of itch such findings are not reproduced, potentially because studies have almost exclusively relied on histaminergic itch provocations not mimicking itch in AD [14,48]. While studies on itch in response innocuous thermal stimulation in AD are inconclusive, heat algoknesis has been documented in patients with AD. Heat stimuli in the noxious range applied in lesional skin of patients with AD have been shown to induce itch even when such stimuli were consistently rated as evoking only heat pain in the healthy controls [65]. Similar observations have been made in a human model of contact dermatitis itch [111]. For electrically induced itch the evidence is contradictory, with studies showing both no differences in itch ratings between chronic itch patients vs. healthy controls, as well as studies showing significant sensitization in itch patients [66,78,162]. Itch sensitization to chemical provocations with pruritogens [10,67,144] is the most studied phenomenon. While it is beyond the scope of the current review to summarize this extensive literature, it appears that evidence supports at least two central findings: 1) there is limited sensitization to histaminergic itch provocations, perhaps beyond mild sensitization occurring intra-lesionally [67,143,144], and 2) recent studies indicate increased intra- as well as extra-lesional sensitivity to cowhage-evoked itch [10,56,113]. However, a systematic assessment of studies on sensitization to various chemical itch provocations in chronic itch patients is needed before more definite conclusions can be drawn. Notably, algoknesis to chemical pain provocations is well documented. In lesional skin of patients with AD common algogens such as acetylcholine [60], low pH-solution [65] and bradykinin [63] predominantly evokes itch whereas they mostly or exclusively evokes pain in healthy controls. Conversely, histamine, which is considered a quintessential pruritogen, has been shown to acts as an algogen in patients with chronic post-herpetic neuralgia [25]. Pruriceptive C-nociceptors are prone to tachyphylaxis after repeated chemical stimulations [3,85]. Hence, in

chronic inflammatory itch conditions, sensitization of pruriceptive units probably include mechanisms by which tachyphylaxis is counteracted, which would contribute to maintaining prolonged itch exacerbations. A proposed mechanism hereof is that local tissue acidosis (associated with inflammation) enhances pruriceptive signaling by co-opting acid-sensing ion channel 3 [70].

5.4 The potential implications of measuring itch sensitization: For many patients with chronic itch, allo- and hyperknesis are highly bothersome symptoms that prompt, maintain or worsen scratch bouts and impose behavioral restrictions, including avoidance of wearing certain fabrics or staying away from warm environments [10,28,34,141]. It is not clinically feasible to implement microneurographic recordings from peripheral neurons and assessing sensitization directly in spinal nociceptive circuitry is impossible in humans. Instead, by using QST, the severity and spatial extent of itch dysesthesias and hypersensitivity to various sensory stimuli can be psychophysically measured in individual patients [8,10,65,144]. Based on case descriptions, mapping of allo/hyperknesis has been found useful as a means to locate an itch hypersensitive area on normally appearing skin [7,15].

Within the pain research area, assessment of sensitization using standardized QST and advanced sensory paradigms, such as temporal summation of pain and conditioned pain modulation, have been shown to be useful for instance in predicting treatment response to pharmaceutical and surgical interventions [24,46,115,157]. Notably, recent studies have shown that mechanistic subgrouping of neuropathic pain patients based on assessment of, e.g., mechanical and thermal hyperalgesia may result in improved treatment response rates [46,93]. Such studies have not yet been undertaken in patients with chronic itch, but it is clear that centrally acting antipruritics can be of use in otherwise refractory patients [40,116]. Moreover, a recent study proposed that prolonged itch and micro-vascular reactions to cowhage and histamine provocations might act as diagnostic indicators of AD, being of potential value in atypical/mild cases [56]. Currently, the clinical utility of assessing alloknesis and hyperknesis as well as itch sensitization in general (e.g. sensitization to chemical provocations) remains to be explored. Antipruritic therapeutic measures should focus on reducing local inflammation and targeting the underlying cause when possible. In contrast to chronic pain, chronic itch is mainly regarded as a symptom of an underlying disease rather than as a disease itself. However, chronic itch also presents in absence of any recognized disease processes, in which case it is often denoted as chronic idiopathic pruritus [29,153]. Disease measures such as lesional severity in AD correlates surprisingly poorly with the itch and cutaneous pain that the individual patients report [41,146]. An analogue mismatch between pathological findings and pain symptoms is commonly observed in pain conditions [19,50]. It could be hypothesized that chronic itch patients with inflammatory dermatoses displaying no signs of itch sensitization, for instance no allo-/hyperknesis nor increased

responses to chemical provocation in non-lesional skin, would respond adequately to peripherally acting anti-inflammatory and immune-modulatory drugs. On the other hand, patients exhibiting significant intra- and extra-lesional itch sensitization, could benefit more from additional therapeutics inhibiting central itch processing as well as sensitization [67]. Evidence from the pain field suggests that centrally acting pharmacotherapy inhibiting central hyper-excitability in addition to cognitive behavioral-, stress-relief- or exercise therapies might be effective in reducing sensitization. Relevant pharmaceuticals include NMDA-receptor antagonists, opioids, tricyclic antidepressants, selective-serotonin reuptake inhibitors (SSRI), serotonin noradrenaline reuptake inhibitors and gabapentinoids [23,24,39,105]. Notably, despite a scarcity of RCTs with itch relieving drugs, both SSRIs and gabapentinoids have antipruritic effects in certain itch conditions while opioids (μ-agonists) are well known to induce itch [116]. Several studies have associated psychophysical measures of pain sensitization with treatment outcome following both pharmaceutical and surgical interventions [46,93,115,157]. Such data is currently lacking in the context of itch and it is unclear whether similar mechanistic inferences can be drawn from itch sensitivity testing. While alloknesis and hyperknesis are commonly referred to as prominent features of chronic itch conditions [124,134], they have thus far only been sparsely studied in other chronic itch patients groups than AD [59,65,75,77,144]. Assessing the clinical utility of itch sensitivity quantification requires developing a standardized, compact psychophysical test battery designed to detect and measure itch sensitization in patients [92]. Such tests need to be based on, and optimized in accordance with, advances in our mechanistic understanding of itch and itch sensitization to mechanical and other types of stimuli. Concerns have recently been expressed regarding the degree to which the nociceptors responsible for spontaneous pain, for instance in neuropathic conditions, are specifically testable with currently applied sensory assessment protocols [32,126]. Data from pain patient cohorts obtained by QST paradigms such as sensory pain thresholds does only occasionally correlate well with the reported clinical pain [118,126,133,157]. As similar caveats might adhere to itch sensitivity assessments, it is by no means a foregone conclusion that sensory testing is clinically useful in the context of chronic itch.

6. Conclusion

Cutaneous dysesthesias associated with itch and pain are strikingly similar, and can be assessed by similar sensory testing techniques, acting as proxy measures of sensitization. For pain, assessment of allodynia and hyperalgesia are ubiquitous in probing the nociceptive system in preclinical, experimental, and clinical settings. Clinically, this may be used to inform/predict responsiveness to treatment. In contrast, assessment of itch-associated dysesthesias has only been marginally studied. Quantifying alloknesis and hyperknesis provides behavioral or psychophysical proxies of itch sensitization which can be performed in animal and human surrogate models of itch, as well as in patients. This review provides a comprehensive overview of: 1) the definitions and purported mechanisms of alloknesis and hyperknesis and their analogy to pain sensitization phenomena; 2) the methods by which alloknesis and hyperknesis can be quantified in preclinical, human experimental and clinical studies; 3) results derived from studies of alloknesis and hyperknesis in chronic itch patients, and; 4) the potential clinical utility and challenges of detecting and measuring itch sensitization. Measuring and distinguishing between alloknesis and hyperknesis with currently available methods is not a trivial task, and much remains unknown regarding neurophysiology of itch sensitization, and the interaction between itch and pain. Psychophysical studies in patients suffering from chronic itch have repeatedly shown mechano-sensory aberrations compatible with itch sensitization. However, these phenomena have only been sparsely documented in diseases other than AD. Further research needs to examine the mechanisms of itch sensitization, how current assessment methods can be optimized, why sensitization characteristics are pronounced only in certain patients within the same itch condition, and whether these psychophysical tests can be utilized clinically.

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Figure legends

Figure 1 – Conceptual illustrations of the sensitized state constituting alloknesis (A), hyperknesis and algoknesis (B). A) Alloknesis comprises a switch in perception of a normally innocuous stimulus such as light stroking of the skin, which additionally or alternatively becomes itch evoking. **B**) Hyperknesis comprises a leftward shift in the stimulus-response curve for a normally itching stimulus while the modality-switch phenomenon in which a predominantly pain-evoking stimulus is perceived as itching is herein referred to as 'algoknesis' (marked with §). The stimulus intensity scale (marked with *) on the x-axis of plot A is not continuous and far from all modalities evoke both itch and pain.

Figure 2 – Models of itch sensitization mechanisms occurring in the periphery and in the spinal dorsal horn. Lightning bolts denotes components of the modeled pathways where sensitization may occur. Potential sites of disinhibition are marked with red stop-symbols. **A**) Following a barrage from a pruriceptive primary afferent (red) a facilitatory interneuron (green) that receives convergent input from an Aβ-fiber (blue), becomes sensitized. Consequently, the pruriceptive projection neuron exhibit responsiveness to light touch stimuli, such as brush strokes, leading to the abnormal perception of itch (alloknesis). **B**) Following a barrage from a pruriceptive primary afferent (red) a facilitatory interneuron (green) that receives convergent input from a mechanosensitive nociceptor (blue), becomes sensitized. Consequently, the pruriceptive projection neuron exhibit increased responsiveness to pinprick stimuli, leading to de novo or increased perception of itch in conjunction with the normal pricking sensation. A notable distinction between **A**) and **B**) is that for **B**) primary hyperknesis could be mediated by sensitization of the pruriceptive primary afferent (red) itself by increased sensitivity to pinprick stimuli or by direct convergence of the mechanosensitive nociceptor. **C**) Histamine-induced pruriception engages an inhibitory interneuron (green) below threshold potential, which in turn becomes receptive to input from mechano-nociceptive units (blue). Subsequently, a noxious counter-stimulus such as scratching inhibits signaling from the pruriceptive projection neuron (adapted from "and-gate" model [42]). Note that scratch-induced inhibition of pruriceptive STT neurons occur in a state-dependent manner, i.e. inhibition only occurs during pruritogen-evoked activity, but not during spontaneous or algogen-evoked firing (shown for histamine) [44]. In chronic itch conditions indirect evidence suggest that scratch-evoked itch inhibition is blunted [69,127]. Such a blunting of normal itch inhibition could result from: disinhibition of the depicted spinal circuitry, loss of epidermal nerve fiber density resulting in decreased input to the gate (reduced fiber density is a frequent finding in chronic itch conditions), or involve altered of supraspinal modulation (not depicted). While the stimuli examples given above are derived from human surrogate itch model studies the initial driving itch might as well be "endogenous" pruriceptive signaling, e.g. associated with atopic dermatitis, neuropathic itch etc.

Figure 3 – The inter-variability of hyperknesis in patients with atopic dermatitis compared with data from healthy controls. The full study, including the methodology used to assess and rate hyperknesis, and a simplified depiction of this data has been published elsewhere [10], *reproduced with permission*. **A**) Shows the inter-variability of

hyperknesis probed at baseline in lesional (dark red) and non-lesional (bright red) skin of patients with atopic dermatitis (n = 25) compared to healthy controls (n = 25). Data from homologous healthy control areas is pooled (50 data points). **B**) Shows the same as (**A**), but here hyperknesis was assessed after itch from a cowhage provocation had subsided (again conducted intra and extra-lesionally). Bottom plots shows the intra-lesional responses to mechanical itch provocations correlated with the responses to extra-lesional provocations at baseline (**C**) and following a cowhage provocation (**D**). Marked grey areas indicate the healthy control average +2 standard deviations (SD), thus constituting a limit at which hyperknesis on an individual level can be detected. Note that significant individually determined hyperknesis only affects 20-52% of the patients depending on the assessment method (>1.96 SDs above the average healthy control response) and that patients either have sensitization restricted to their lesions or affecting both their lesional and non-lesional skin. Only n = 1/50 showed sensitization selectively in non-lesional skin.

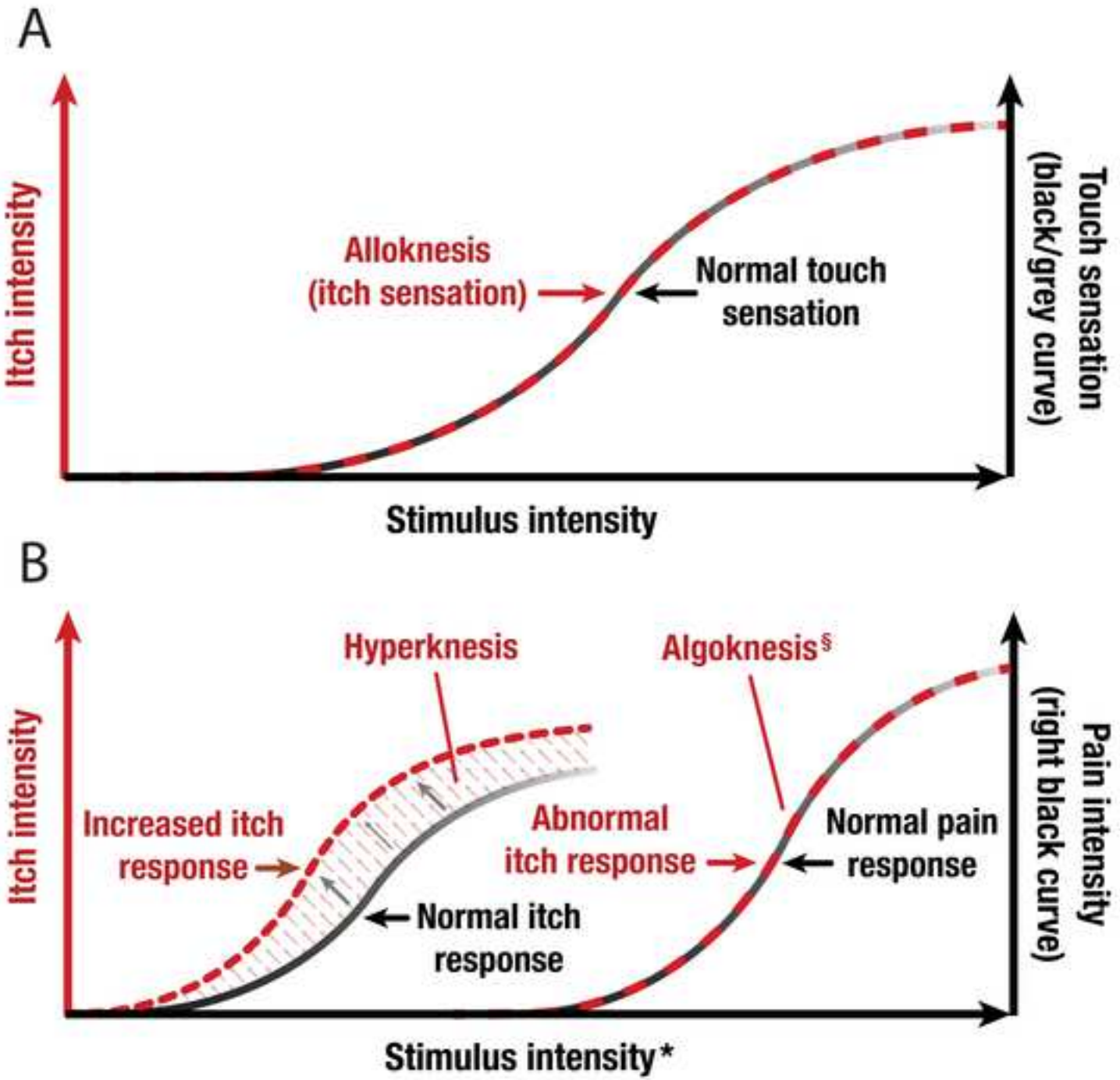

Figure 2_revised

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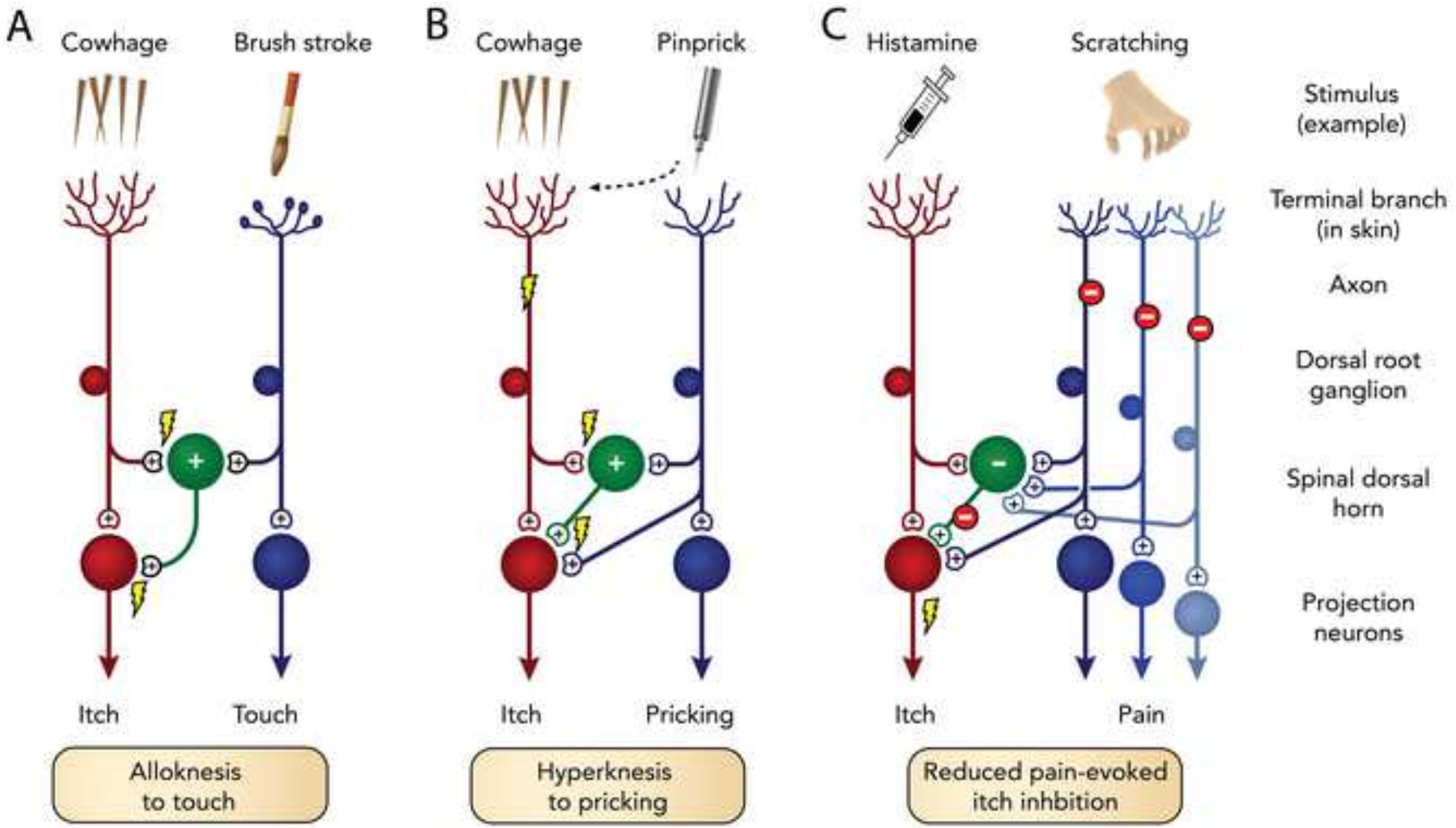

Figure 3

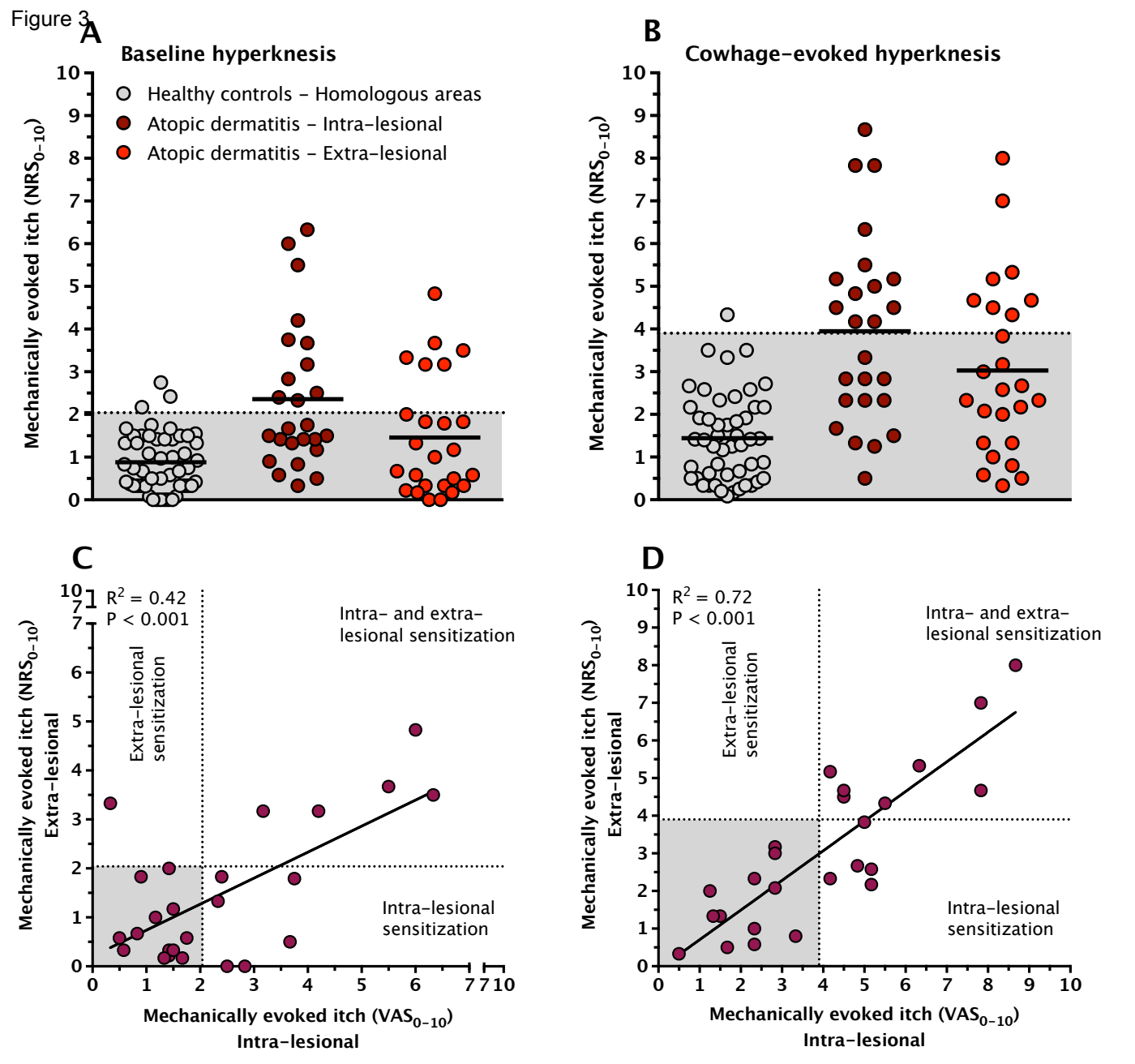
A
Baseline hyperknesis
Healthy controls – Homologous areas
Atopic dermatitis – Intra-lesional
Atopic dermatitis – Extra-lesional
Mechanically evoked itch (NRS0-10)
B
Cowhage-evoked hyperknesis
Mechanically evoked itch (NRS0-10)
C
R2 = 0.42
P < 0.001
Intra- and extra-lesional sensitization
Extra-lesional sensitization
Intra-lesional sensitization
Mechanically evoked itch (NRS0-10) Extra-lesional
Mechanically evoked itch (VAS0-10) Intra-lesional
D
R2 = 0.72
P < 0.001
Intra- and extra-lesional sensitization
Extra-lesional sensitization
Intra-lesional sensitization
Mechanically evoked itch (NRS0-10) Extra-lesional
Mechanically evoked itch (VAS0-10) Intra-lesional

Table 1

Sensory phenomenon	Descriptor(s) (Proposed usage)	Suspected peripheral input	Sensitization processes		Examples of studies
			Peripheral	Central	
Touch / brush strokes / fabric -evoked itch	Alloknesis[1] (Tactile)	Aβ-fibers		X	63,131,144
Pinprick-evoked itch / reduced thresholds hereto	Hyperknesis (Pinprick)	[Aδ/PmC-fibers]	[X]	X	10,65,75
Warmth induced / aggravated itch	N/A (Warmth alloknesis[1])	[Warm C-fibers/ PmC-fibers]	[X]		5,10,65,102
Heat-evoked itch	N/A (Heat algoknesis[2])	[Aδ/PmC-fibers]	[X]	[X]	5,65,102,111
Increased itch in response pruritogens	Hyperknesis (Chemical)	C-fibers (CMi and PmC)	X	[X]	10,56,67,144

Table 1 – Itch sensitization phenomenon and proposed mechanisms. Square bracket "[]" indicates conceivable, but not yet established, mechanisms. CMi = C-mechano-insensitive fibers, PmC = Polymodal C-fibers. [1] Principally, alloknesis could occur to non-mechanical stimuli, such as gentle warming, but this example is not yet well established mechanistically. [2] Algoknesis is used in the present review to denote itch occurring in response to stimuli, which are under normal circumstances predominantly pain-evoking.

Table 2

	Provocations / causative condition(s)	Mechanical itch dysesthesia	Assessment techniques / signs	Example of studies
Animals models	Pruritogen injections, dry skin, contact dermatitis, psoriasis model, atopic dermatitis model, genetic models	Alloknesis	Low intensity von Frey filaments or brush	1,4,33,61,88,122,145
		Hyperknesis	N/A [Medium intensity von Frey filaments or pinprick (≈ mechanical pain threshold)]	None
Human models	Pruritogens (e.g. histamine, cowhage) electrical/mechanical stimulation, contact dermatitis model	Alloknesis	Brush strokes (mapping or single stimuli), von Frey filaments or cotton wisp	63,66,111,128
		Hyperknesis	Weighted needles (sharp), von Frey filaments	11,66,111
Clinical itch conditions	Atopic dermatitis, renal insufficiency associated pruritus, post-burn pruritus contact dermatitis, neuropathic itch	Alloknesis	No preceding itch provocation: e.g. to wool, brush strokes, synthetic fabrics etc., After itch provocation: brush strokes, cotton swab/wisp, von Frey filaments	15,63,107,144,147
		Hyperknesis	No preceding itch provocation: wool, pinprick stimulators. After itch provocation: Pinprick stimulators (blunt), weighted needles (sharp), von Frey filaments	10,65,75,78,144

Table 2 – Methodology used to assess mechanical itch dysesthesias. The table provides and overview of methods by which alloknesis and hyperknesis have been studied in animals, human experimental models and in patients suffering from chronic itch diseases. In the row *clinical itch conditions*, "no preceding itch provocation" refers to assessment of allo/hyperknesis without any eliciting itch provocation, while "after itch provocation" refers to assessment of the itch dysesthesia following an itch provocation. Square brackets denote a potential method not yet thoroughly explored.

Table 3

Study	Itch condition	Assessment methodology	Observed mechanical itch dysesthesia	
			Lesional	Non-lesional
Wahlgren et al. 1990 [144]	AD	Wool fibers (Intensity approach)	No preceding itch provocation: ↑ Hyperknesis Unclear whether lesional and/or extra-lesional	
Heyer et al. 1995 [59]	AD	Sensory brush (Spatial approach[1])	N/A	After itch provocation: ↓ Alloknesis
Weisshaar et al. 1998 [149]	AD	Sensory brush (Spatial approach[1])	N/A	After itch provocation: ↓ Alloknesis
Weisshaar et al. 2003 [147]	Renal insufficiency	Sensory brush (Spatial approach[1])	N/A	After itch provocation: →Alloknesis
Ikoma et al. 2004 [65]	AD, psoriasis	Weighted needle stimulators (Intensity approach)	No preceding itch provocation: ↑ Hyperknesis (AD) → Hyperknesis (psoriasis)	No preceding itch provocation ↑ Hyperknesis (peri-lesional)[4] → Hyperknesis (extra-lesional)[4]
Ikoma et al. 2005 [66]	AD	Sensory brush and pin prick stimulators (Spatial approach[2])	N/A	Evoked: → Alloknesis Evoked: → Hyperknesis[5]
Hosogi et al. 2006 [63]	AD	Sensory brush (Intensity approach)	No preceding itch provocation: ↑ Alloknesis	No preceding itch provocation: →Alloknesis
Laarhoven et al. 2007 [75]	AD	Von Frey stimulators (Intensity approach)	No preceding itch provocation: ↑ Hyperknesis[3]	No preceding itch provocation: ↑ Hyperknesis[4]
Andersen et al. 2017 [10]	AD	Von Frey stimulators (Intensity approach)	No preceding itch provocation: ↑ Hyperknesis	No preceding itch provocation: ↑ Hyperknesis

Table 3 – Results from studies on mechanical itch dysesthesias in patients with chronic itch versus healthy controls. The table list notable studies assessing alloknesis and/or hyperknesis in patients with itch conditions as well as the methods applied in each study. Notice that the vast majority of studies have been conducted in atopic dermatitis (AD). **Caption**: [1] = Following an iontophoretic histamine provocation, [2] = Following electrically induced itch, [3] = predominantly intra-lesional, [4] = in AD only, [5] = a trend toward more hyperknesis in patients was observed, [6] = predominantly non-lesional. **Arrows**: sensitivity in patients vs. controls: ↑ = significantly increased responses in patients ↓ = significantly decreased responses in patients, → no significant differences. "No preceding itch provocation" refers to assessment of allo/hyperknesis without any preceding itch provocation, while "after itch provocation" refers to assessment of the itch dysesthesia following an itch provocation