The Bayesian brain in imbalance: Medial, lateral and descending pathways in tinnitus and pain: A perspective

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Abstract

Tinnitus and pain share similarities in their anatomy, pathophysiology, clinical picture and treatments. Based on what is known in the pain field, a heuristic model can be proposed for the pathophysiolgy of tinnitus. This heuristic pathophysiological model suggests that pain and tinnitus are the consequence of an imbalance between two pain/tinnitus evoking pathways, i.e., a lateral sensory pathway and a medial affective pathway, both of which are not balanced anymore by a pain/noise inhibitory pathway. Mechanistically, based on the Bayesian brain concept, it can be explained by a switch occuring under influence of the rostral to dorsal anterior cingulate cortex of its prior predictions, i.e., a reference resetting, in which the pain/tinnitus state is considered as the new reference state. This reference resetting is confirmed by the nucleus accumbens as part of the reward system and maintained by connectivity changes between the nucleus accumbens and the pregenual anterior cingulate cortex. As a consequence it can be suggested to treat pain/tinnitus via reconditioning, either surgically or non-surgically. The model can also be used to develop objective measures for tinnitus and pain via supervised machine learning.

Keywords

Pain, Tinnitus, Analogy, Lateral, Medial, Inhibitory, Balance, Bayes, Imbalance

1 Introduction

Chronic tinnitus and chronic pain can be defined as non-complex sensory experiences with an associated affective component in the absence of a corresponding external stimulus. As such, they can be considered phantom perceptions, which can occur in any sensory domain. The vast majority of phantom perceptions relate to the somatosensory (chronic pain) or to the auditory system (chronic tinnitus) (De Ridder et al., 2011b), and are perceived in the deafferented area: neuropathic pain it is felt in the area that was initially innervated by the injured nerve (Ramachandran and Hirstein, 1998), while the tinnitus spectrum corresponds to the individual's hearing loss (Norena et al., 2002). Whereas chronic pain is almost always associated with suffering, this is less commonly so in tinnitus. Indeed, about 80% of tinnitus patients do not suffer, or only suffer in a limited way, not driving them to seek medical attention (Axelsson and Ringdahl, 1989; Langguth et al., 2013). This has also limited the development of a definition for tinnitus, and it has been proposed (see chapter "Tinnitus and tinnitus disorder: Theoretical and operational definitions" by De Ridder et al.) that tinnitus is the conscious awareness of a non-complex sound for which there is no identifiable corresponding external sound source, and that a second definition maybe required, for those people who suffer from the tinnitus. Tinnitus with tinnitus-associated suffering could be called tinnitus disorder.

The parallelism between chronic pain and chronic tinnitus was initially based on clinical similarities (Moller, 1997, 2000, 2007; Tonndorf, 1987) and aiming at elucidating the pathophysiology of tinnitus (De Ridder et al., 2011b; De Ridder and Van de Heyning, 2007), which could then lead to novel treaments for chronic tinnitus (De Ridder et al., 2007). However, until recently there were no electrophysiological data to support these claims robustly. A resting state EEG was recorded in a large group of patients during the perception of the tinnitus, in another group of patients during neuropathic pain perception and compared to healthy controls without pain or tinnitus (Vanneste et al., 2019b). Multiple different in depth analyses were performed, including Fast Fourier transformations, conjunction analysis, microsegmentation and seed based functional connectivity via lagged phase synchronization, during the tinnitus and pain state (Vanneste et al., 2019b), confirming that the clinical analogy was based on similar underlying pathophysiological mechanisms. Spectral analysis identified similar gamma band activity within the primary auditory and somatosensory cortex for patients with tinnitus or neuropathic pain, respectively. A conjunction analysis furthermore showed an overlap of tinnitus and pain related activity in the anterior and posterior cingulate cortex as well as in the dorsolateral prefrontal cortex in comparison to healthy controls (Vanneste et al., 2019b). Microsegmentation analysis, which decomposes the electrical brain activity into spatiotemporal segments of stable brain states, revealed that both pain and tinnitus patients spent half of the time in one specific microstate,. Microstates are canonical voltage topographies that reflect brief activations of components of resting state brain networks. The dominant microstate in pain and tinnitus is located predominantly in the left anterior midtemporal area, part of the default mode network.

Seed based functional connectivity with the source within this left anterior midtemporal area demonstrated that both delta, alpha and gamma lagged phase synchronization overlap with multiple brain areas of the default mode network between pain and tinnitus, possibly suggesting that the pain and tinnitus were incoprated in their self-representation, i.e., had become part of the self-percept. Yet the area also connected with the salience network, suggestive that the pain and tinnitus were not only part of the self-percept but also maintained in consciousness (Boly et al., 2007; Sadaghiani et al., 2009). For pain and tinnitus to be consciously perceived, the consciousness enabling networks neeed to be co-activated with somatosensory and auditory cortex activity (Boly et al., 2005; Demertzi et al., 2013; Laureys et al., 2000). These consciousness enabling networks involve the self-representational default mode, frontoparietal attention network and salience network (Akeju et al., 2014; Mencarelli et al., 2020). In summary, this study demonstrated that auditory and somatosensory phantom perceptions share an overlapping brain network with common activation and connectivity patterns, and differentiated by specific sensory cortex gamma activation (Vanneste et al., 2019b). In a subsequent purely data driven approach with artificial intelligence identifying commonalities between pain and tinnitus (as well as Parkinson's disease and depression) it was shown that tinnitus and pain share a common beta hyperactivity in the dorsal anterior cingulate cortex and parahippocampus, and are differentiated by theta-gamma cross-frequency coupling (De Ridder et al., 2015b; Llinas et al., 1999) in the auditory cortex and somatosensory cortex, for tinnitus and pain, respectively (Vanneste et al., 2018). Furthermore, the magnitude of the thalamocortical dysrhythmia, characterized by theta-gamma cross-frequency coupling (De Ridder et al., 2011a, 2015b; Llinas et al., 1999; Vanneste et al., 2018), was related to the intensity of the tinnitus and pain (Vanneste et al., 2018). This is in keeping with the fact that it had previously been shown that gamma band oscillations correlate with the intensity of tinnitus (Balkenhol et al., 2013; van der Loo et al., 2009; Vanneste et al., 2017) and pain (Gross et al., 2007). Yet not all studies identify these correlations, and some studies do find the correlation between tinnitus loudness and gamma band activity but not in all patients (Sedley et al., 2012), or related to improvement in general (Adamchic et al., 2014). Thalamocortical dyrhythmia does suggest that tinnitus loudness or painfulness improvement is associated with an increase in alpha (Muller et al., 2013) or decrease in low frequency activity (delta, theta (Graversen et al., 2012)), and in cross-frequency coupling (theta-gamma) (De Ridder et al., 2015a; Vanneste et al., 2018), all of which have been shown to be correlated with tinnitus-matched loudness or painfulness (Vanneste et al., 2018). Thus, the simple gamma-loudness or gamma-pain correlation is likely an oversimplification.

Many resting state EEG and MEG analyses suffer from inherent weaknesses, such as a lack of control for attention, and generally no control for hearing loss or hypoesthesia. And this is important, as for example tinnitus with hearing loss and without hearing loss has some important differences in neural activity as recently demonstrated (Adjamian et al., 2012; Vanneste and De Ridder, 2016; Vanneste et al., 2019a). On the other hand attentional processes may not exert a big influence

on EEG activity in tinnitus (Neff et al., 2019), which does not exclude that connectivity differences may be present. In chronic pain, attention toward pain does induce activity changes, characterized by a decrease in alpha and an increase in gamma band power, localized in the insula (Hauck et al., 2015).

The goal of this munuscript is to propose a heuristic anatomical and physiological framework to further elucidate the shared underlying anatomical and pathophysiological mechanism of chronic pain and chronic tinnitus, which may benefit the development of novel treatment approaches for both pathologies, as well as the construction of an objective measurement for these two entirely subjective states. The brain areas discussed are proposed to be the core areas of three interacting networks, and not limitative. They are selected based on a neurosynth meta-analysis of pain, and a review of the same brain areas in tinnitus.

2 Anatomical similarities between somatosensory and auditory system

Pain is processed by at least three separable pathways, two pain evoking pathways (Bushnell et al., 2013; Price, 2000) and one pain inhibitory pathway (Fields, 2004) (see Fig. 1). The lateral pathway encodes the discriminatory sensory (Bushnell et al., 2013) component, i.e., how painful a stimulus is, the characteristics of the pain (burning, throbbing, …) and the location of the pain. It is a pain specific pathway, in contrast to the medial pathway, which is non-specific, and with the descending inhibitory pathways which are specific but may partially overlap. The medial pathway encodes the motivational/affective component of pain (Bushnell et al., 2013; Craig, 2002; De Ridder and Vanneste, 2016a; Rainville et al., 1997), i.e., the unpleasantness via the rostral anterior cingulate cortex (Rainville et al., 1997), catastrophizing (in migraine) via the anterior insula (Mathur et al., 2016), which combined explain suffering (Wade et al., 2011), as demonstrated clinically and by functional imaging meta-analysis (see Fig. 2). The medial pathway also encodes distress, which is more of an autonomic arousal state (van der Loo et al., 2011), and consequentially drives the attention paid to the pain, as confirmed by cingulotomies, which decrease not only the affective component of pain but also attention paid to pain (Cohen et al., 1999). The medial pathway is non-specific, in that it overlaps with suffering or distress experienced in other pathologies, such as social exclusion (Eisenberger, 2012) and tinnitus (De Ridder et al., 2014a) but also symptoms such as breathlessness (air hunger) (Brannan et al., 2001; Liotti et al., 2001; Parsons et al., 2001; von Leupoldt et al., 2009), hunger (Tataranni et al., 1999), thirst (Denton et al., 1999a, b; Farrell et al., 2008) and others. It is fundamentally a salience pathway (Seeley et al., 2007) that attaches a behavioral relevance to the pain and tinnitus, and maintains the pain and tinnitus into consciousness (Boly et al., 2007; Sadaghiani et al., 2009). The pain inhibitory pathway suppresses ongoing pain in a state dependent manner (Fields, 2004) and determines the presence (Moens et al., 2012; Watanabe et al., 2018), i.e., most likely the duration of chronic neuropathic pain during the day, analogous to what is known in tinnitus (Song, 2015). The medial and lateral pain

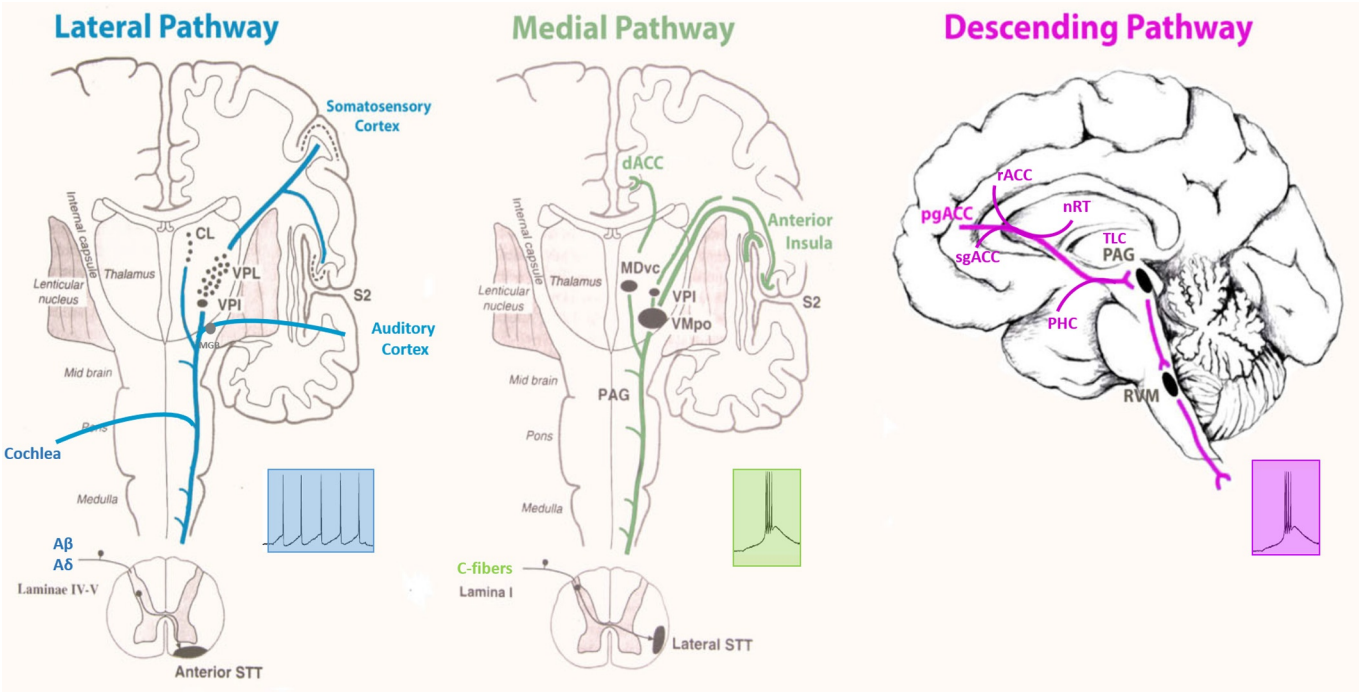

FIG. 1

The anatomical analogy between the somatosensory and auditory system. Both systems are characterized by a domain-specific discriminatory sensory component (blue), a non-specific affective/motivational component (green) and a parallel descending inhibitory component (pink).

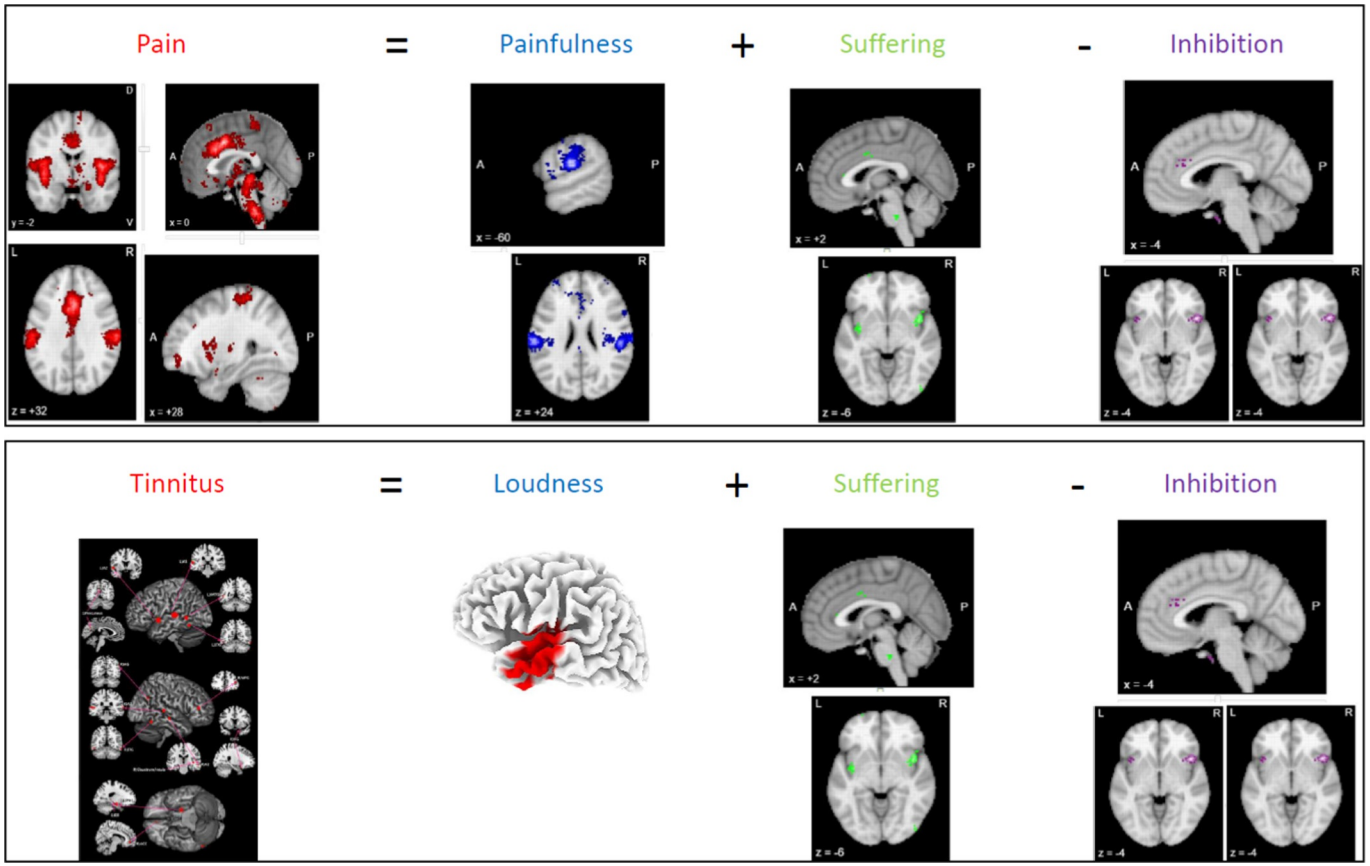

FIG. 2

Global pain consists of painfulness with an associated amount of suffering present during a certain amount of the time.

pathways are processed in parallel (Frot et al., 2008), and can be individually modified without affecting the other pathway (Bushnell et al., 2013), as evidenced by both cingulotomies/lobotomies (Freeman and Watts, 1950), in which the unpleasantness is removed but the intensity remains the same and the fact that mood influences the unpleasantness but not the intensity of the pain (Bushnell et al., 2013; Villemure and Bushnell, 2009). But also oppositely, distraction can reduce pain intensity without decreasing unpleasantness (Bushnell et al., 2013).

The ascending medial system is activated by C-fibers and connects to the mediodorsal and ventromedial posterior nuclei of the thalamus which relay the ascending sensory information to the rostrodorsal anterior cingulate cortex and anterior insula (Craig, 2002, 2004; Price, 2000). The ascending lateral pain pathway is predominantly activated by Aδ- and Aβ-fibers and connects to the ventral posterolateral nucleus of the thalamus and reaches the somatosensory cortex and parietal area (Craig, 2002; Price, 2000). The descending pain inhibitory system involves the rostral and pregenual anterior cingulate cortex and connects to the reticular nucleus of the thalamus, and periaqueductal gray and from there is relayed further to the somatosensory periphery via the ventrolateral medulla oblongata (Craig, 2002; Fields, 2004; Kong et al., 2010) and involves also the (para)hippocampal area (Kong et al., 2010) (Fig. 1).

Pain is context dependent (Carlino et al., 2014), as exemplified by placebo analgesia (Carlino et al., 2014), and the fact that pain can be unpleasant or pleasant depending on the context (Leknes et al., 2013). Relative relief of pain can be perceived as pleasant (Leknes et al., 2013), but the context dependence is very clear in sadomasochistic pain, in which pain can be perceived as pleasant, but only and uniquely in its specific sexual content (Kamping et al., 2016). Pleasant pain is mediated via activation of the descending pain inhibitory pathway, whereas unpleasant pain is processed via the medial pain system (Leknes et al., 2013; Rainville et al., 1997).

Pain can lead to perceived disability, which is predominantly related to the suffering or catastrophizing (Kovacs, 2011), and less so to the painfulness (Garbi Mde et al., 2014). It has indeed been shown that the perceived pain disability strongly correlates with the affective component of the pain, especially catastrophizing (Kovacs, 2011), whereas the association with painfulness is only weak (Garbi Mde et al., 2014). Even more, 40% of the total effect of pain severity on functional disability is mediated by pain catastrophizing (Besen et al., 2017).

The auditory system is organized in a very similar way as the somatosensory system. The separation between the medial and lateral system may be less clear, even though anatomically the medial auditory pathway appears to be very similar to the medial pain pathway. Indeed, the medial system is activated by sounds as well (Iannetti and Mouraux, 2010; Legrain et al., 2011; Mouraux et al., 2011), and the pathways largely overlap (Langers and Melcher, 2011) with the medial pain pathways. This also explains why the dorsal anterior cingulate cortex is involved in both pain and tinnitus, as demonstrated by a machine learning approach looking at the commonalities between pain and tinnitus (Vanneste et al., 2018). This furthermore

explains that both chronic pain and tinnitus were treated with frontal lobotomies resulting in the same outcome: especially improved suffering without changing painfulness or tinnitus loudness (Beard, 1965; Elithorn, 1953; Freeman and Watts, 1950).

For tinnitus, the separation between the medial and lateral pathway is less obvious than for pain. The auditory cortex, part of the lateral sensory pathway is also involved in affective processing (Schecklmann et al., 2013), and the anterior cingulate cortex and insula, part of the affective pathway are also related to tinnitus loudness perception (De Ridder et al., 2015a). A possible explanation is based on the fact that tinnitus loudness and tinnitus distress correlate (Bruggemann et al., 2016; Hiller and Goebel, 2006; Probst et al., 2016; Wallhausser-Franke et al., 2012). Therefore, loudness and distress may obviously correlate with the same brain areas. Yet, it cannot be excluded that tinnitus loudness and distress encoding areas truly overlap. Transcranial magnetic stimulation (Vanneste et al., 2011), transcranial direct current stimulation (Vanneste and De Ridder, 2011) and implants (De Ridder et al., 2016) of the dorsal anterior cingulate cortex all modulate both the tinnitus loudness perception and the affective component, in keeping with the functional imaging literature.

The descending auditory inhibitory pathways, also known as the noise canceling pathways, can be reconstructed based on the published literature. Analogous to the descending pain inhibitory pathways, the pre-to subgenual anterior cingulate cortex is involved (Leaver et al., 2011; Rauschecker et al., 2010; Seydell-Greenwald et al., 2012). It has been hypothesized that this connects to the reticular nucleus of the thalamus (Leaver et al., 2011; Rauschecker et al., 2010). However, how this inhibitory pathway connects to the olivocochlear bundle is less obvious. Recently the tectal longitudinal column (De Ridder et al., 2012; Marshall et al., 2008; Saldana et al., 2007) has been discovered, adjacent to the periaqueductal gray, and involved in sound suppression (De Ridder et al., 2012; Marshall et al., 2008; Saldana et al., 2007). The tectal longitudinal column connects to the olive (Vinuela et al., 2011), from where the well-studied olivocochlear bundle transmits inhibitory information to the cochlea (Attanasio et al., 1999; Moore et al., 1999).

In summary, based on the existing literature about the anatomy and physiology it can easily be proposed that the somatosensory system and auditory system are very similar in structure and function, as visually represented in Fig. 1.

3 Pain and tinnitus as an intracranial balance problem

Pain can be regarded as a balance between pain input and pain suppression. When pain input equals suppression no pain is perceived, but when input is increased and/or suppression is decreased, pain ensues. This has been well described as the pain gate at the level of the spinal cord (Tataranni et al., 1999) and can be conceptualized at the level of the brain as well (De Ridder et al., 2011a).

When a patient calls on a healthcare professional to treat his or her pain, the patient will tell he or she is in pain. This means that the patient has a certain amount of painfulness associated with a certain amount of suffering, present during the day

during a certain amount of time. Each of these three components can be related to one of the three abovementioned pathways: the lateral painfulness pathway, the medial suffering pathway and the descending perceptual pathway. Each of these three components can be scored using a simple numeric rating scale for pain and suffering and a percentage of the day that the pain is dominantly present. This separation in three components linked to the three pathways can be objectified by a neurosynth meta-analysis of 420 fMRI studies (www.neurosynth.org), indeed confirming that in chronic pain all three pathways are involved (Fig. 2).

Similarly, when a patient with tinnitus calls on a healthcare professional to treat his or her tinnitus, the patient will tell he or she has tinnitus. This means that the patient perceives the phantom sound with a certain amount of loudness associated with a certain amount of suffering, present during the day during a certain amount of time. Also, of these three components can be related to one of the three abovementioned pathways: the lateral loudness pathway, the medial suffering pathway and the descending perceptual pathway. Each of these three components can be scored using a simple numeric rating scale for loudness and suffering and a percentage of the day that the pain is dominantly present.

In pain, using EEG, one can compute a balance between the three pathways by selecting one area as main hub for each pathway: the somatosensory cortex activity as a proxy for the lateral pain specific ascending pathway, the dorsal anterior cingulate cortex activity as a proxy for the medial suffering pathway and the pregenual anterior cingulate cortex activity as a proxy for the descending pain inhibitory pathway. Using source localization with sLORETA, the current density, i.e., the amount of activity, can be computed in the pregenual anterior cingulate cortex, the dorsal anterior cingulate cortex and the somatosensory cortex, and the balance between the areas can be computed using the formula "pain = current density (dorsal anterior cingulate cortex + somatosensory cortex)/2x current density pregenual anterior cingulate cortex," which reflects the balance of the activity between the two pain input pathways and the one descending pathway (Fig. 3). This balance, computed by recording the source localized EEG activity of the somatosensory cortex, dorsal anterior cingulate cortex and pregenual anterior cingulate cortex indeed correlates with the presence and intensity of the pain (Fig. 3).

A balance can only develop if there is communication between these three areas. Communication in the brain between different areas can be visualized by computing functional connectivity and effective connectivity. Functional connectivity is a statistical measure of coherence, i.e., co-varying activity or phase synchronization between two areas in the brain. Functional connectivity consists of a combination of instantaneous and lagged phase synchronization. However, instantaneous phase synchronization is highly contaminated by volume conduction of the electrical activity in the scalp. In order to remove spurious false positive connections, the instantaneous phase synchronized activity is therefore removed from the computation, leaving only lagged phase synchronization. The lagged phase synchronization between the pregenual anterior cingulate cortex, dorsal anterior cingulate cortex and somatosensory cortex reflects the communication between those areas.

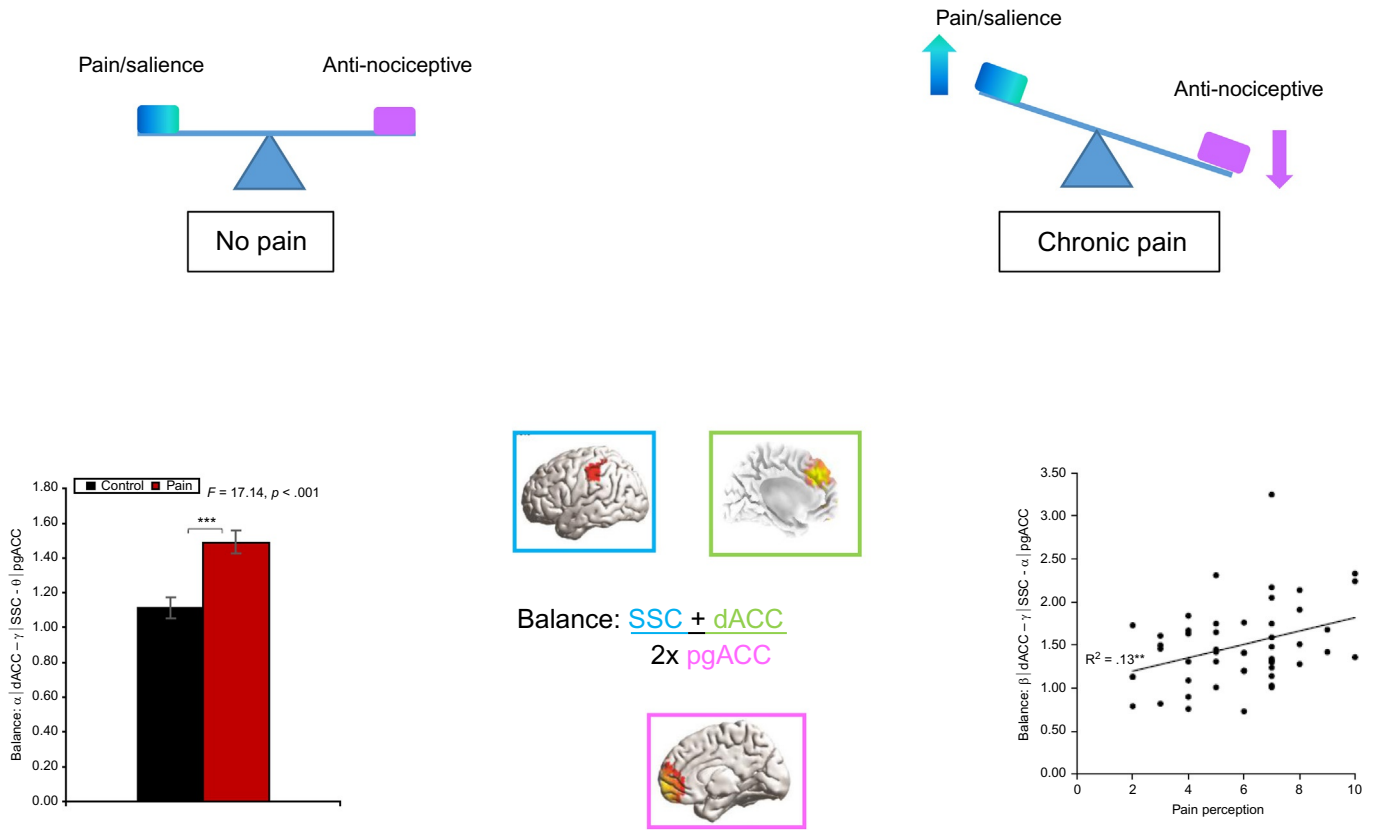

FIG. 3

chronic pain is the balance between two pain evoking pathways (lateral and medial) and the pain inhibitory pathway. The balance can be computed using the current of the main hubs of each pathway, i.e., the somatosensory cortex (SSC) for painfulness, the rostral to dorsal anterior cingulate cortex (dACC) for suffering and the pregenual anterior cingulate cortex (pgACC) for pain inhibition. The presence of pain is characterized by a balance >1, i.e., more pain evoked or less pain suppressed or a combination. The amount of pain correlates with the amount of imbalance.

And, in chronic pain, it has been shown that the communication between the three areas, i.e., pathways is reduced in comparison to healthy controls without pain. Thus, the pain input and pain suppression become uncoupled, leading to an imbalance, i.e., pain. However, functional connectivity does not explain from where to where in the brain the communication is disturbed. Effective connectivity, e.g., by applying Granger causality computation can be used to show the direction of the functional connectivity. And, in healthy controls without pain it appears that the pregenual anterior cingulate cortex sends information to the dorsal anterior cingulate cortex and somatosensory cortex, i.e., the pregenual anterior cingulate cortex appears to suppress activity in the dorsal anterior cingulate cortex and somatosensory cortex, preventing pain to arise by maintaining a balance between pain input (dorsal anterior cingulate cortex + somatosensory cortex) and pain suppression (pregenual anterior cingulate cortex). In contrast, in chronic pain, the effective connectivity is disturbed, with the dorsal anterior cingulate cortex sending, most likely inhibitory, information to the pregenual anterior cingulate cortex (Fig. 4).

Considering the analogy between the somatosensory and auditory system it can be hypothesized that in tinnitus a similar mechanism is at work, in which tinnitus is the result of an imbalance between the rostral anterior cingulate cortex, auditory cortex and pregenual anterior cingulate cortex. This is in keeping with a previously proposed model (De Ridder et al., 2014a), which attempted to reconcile the noise canceling deficiency model of tinnitus (Leaver et al., 2011; Rauschecker et al., 2010) and the deafferentation based models of tinnitus (De Ridder et al., 2014a; Llinas et al., 1999). However, it has been hypothesized that in tinnitus there are likely two different pathophysiological mechanisms, one for tinnitus with hearing loss, and one for tinnitus without hearing loss (De Ridder et al., 2014b; Vanneste and De Ridder, 2016; Vanneste et al., 2019a). Whereas tinnitus without hearing loss involves the pregenual anterior cingulate cortex, tinnitus with little hearing loss involves the auditory cortex, and tinnitus with more severe hearing loss involves the parahippocampus (De Ridder et al., 2014b; Vanneste and De Ridder, 2016; Vanneste et al., 2019a), the main hub of auditory memory (De Ridder and Vanneste, 2014; De Ridder et al., 2006; Laureano et al., 2014). Thus, the imbalance may be computed differentially for tinnitus with and without hearing loss.

4 What controls the imbalance?

Based on the Opponent-Process theory (Solomon and Corbit, 1973, 1974) the reward system can be simplified as a balance between positive and negative reward (Elman et al., 2013), hypothetically computed by the ventral tegmental area. The main hub of the positive reward system is the nucleus accumbens, which connects to the ventral tegmental area via the laterodorsal tegmentum. The main hub of the negative reward is the lateral habenula. Indeed, activation of inputs to the ventral tegmental area from the laterodorsal tegmentum and the lateral habenula elicit reward and aversion in mice, respectively (Lammel et al., 2012). Laterodorsal tegmentum neurons

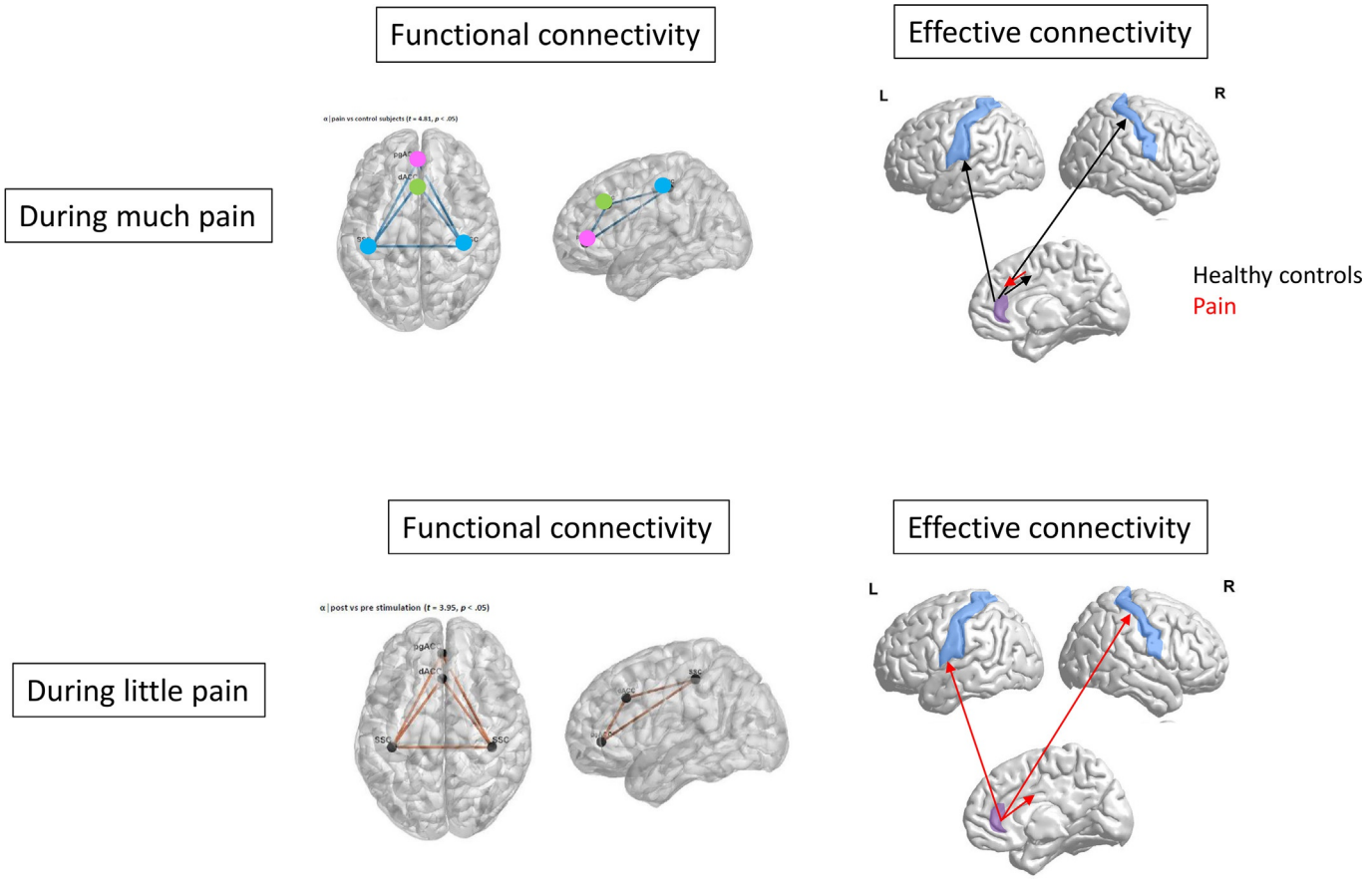

FIG. 4

During pain the functional connectivity between the three pathways is decreased, suggesting the three pain related areas do not communicate, losing the normal pain balance. With less pain, there is more communication, suggesting the balance is regained. The culprit of pain is the rostral anterior cingulate cortex, encoding suffering, which suppresses the pain inhibitory pregenual anterior cingulate cortex less. With less pain, the pain inhibitory pregenual anterior cingulate cortex sends (inhibitory) information to the two pain evoking pathways.

preferentially synapse on dopamine neurons projecting to the nucleus accumbens lateral shell, whereas lateral habenula neurons synapse primarily on dopamine neurons projecting to the medial prefrontal cortex as well as on GABAergic neurons in the rostromedial tegmental nucleus. These results establish that the nucleus accumbens and habenula communicate with the ventral tegmental area to generate reward and aversion (Lammel et al., 2012). The connections from the habenula to the ventral tegmental area are glutamatergic, from the nucleus accumbens to the ventral tegmental area GABAergic and from the ventral tegmental area to the habenula and nucleus accumbens dopaminergic (Russo and Nestler, 2013).

The chronification of pain has been linked to the emergence both increased functional (Baliki et al., 2012) and structural connectivity (Mansour et al., 2013) between the nucleus accumbens and the pregenual anterior cingulate cortex. This could be explained as a paradoxical reward associated with the pain (Fig. 5).

The habenula is also connected to the ventral tegmental area, as well as periaqueductal gray, dorsal anterior cingulate cortex and insula, thalamus and somatosensory cortex, all involved in pain processing (Shelton et al., 2012a,b). Furthermore, it receives input from the nucleus accumbens (Shelton et al., 2012a,b), permitting a balance function between nucleus accumbens, ventral tegmental area and habenula.

In tinnitus, the same pathological functional connectivity has been demonstrated between the nucleus accumbens and the pregenual anterior cingulate cortex as well as between the nucleus accumbens and the auditory cortex (Hullfish et al., 2018), suggesting a similar mechanism may be at play. However, in this study no correlation was made with tinnitus chronification, albeit that all patients had chronic tinnitus. Yet, it does suggest that a paradoxical reward may underlie chronic tinnitus as well.

5 Integrating the Bayesian brain with imbalance

Humans and other animals operate in a world of sensory uncertainty (Knill and Pouget, 2004). In phenomenological terms, uncertainty is a state in which a given representation of the world cannot be adopted as a guide to subsequent behavior, cognition, or emotional processing (Harris et al., 2008). As animals move around, resulting in a changing environment, this change implies an inherent uncertainty of what is going to present next in this changing environment (Quartz and Sejnowski, 2002). But apart from environmental uncertainty, there is also processing uncertainty: many factors limit the reliability of sensory information about the world mapping of 3D objects into a 2D image, neural noise in sensory coding, and structural constraints on neural representations and computations (e.g., the density of receptors) (Knill and Pouget, 2004). Our brains must deal with the resulting uncertainty in an efficient way to generate perceptual representations of the world as to guide our actions. This leads to the idea that perception is a process of unconscious, probabilistic inference (Knill and Pouget, 2004).

Based on Helmholtz's active inference concept for vision, also known as the predictive brain, a new model for brain functioning has been proposed, called the

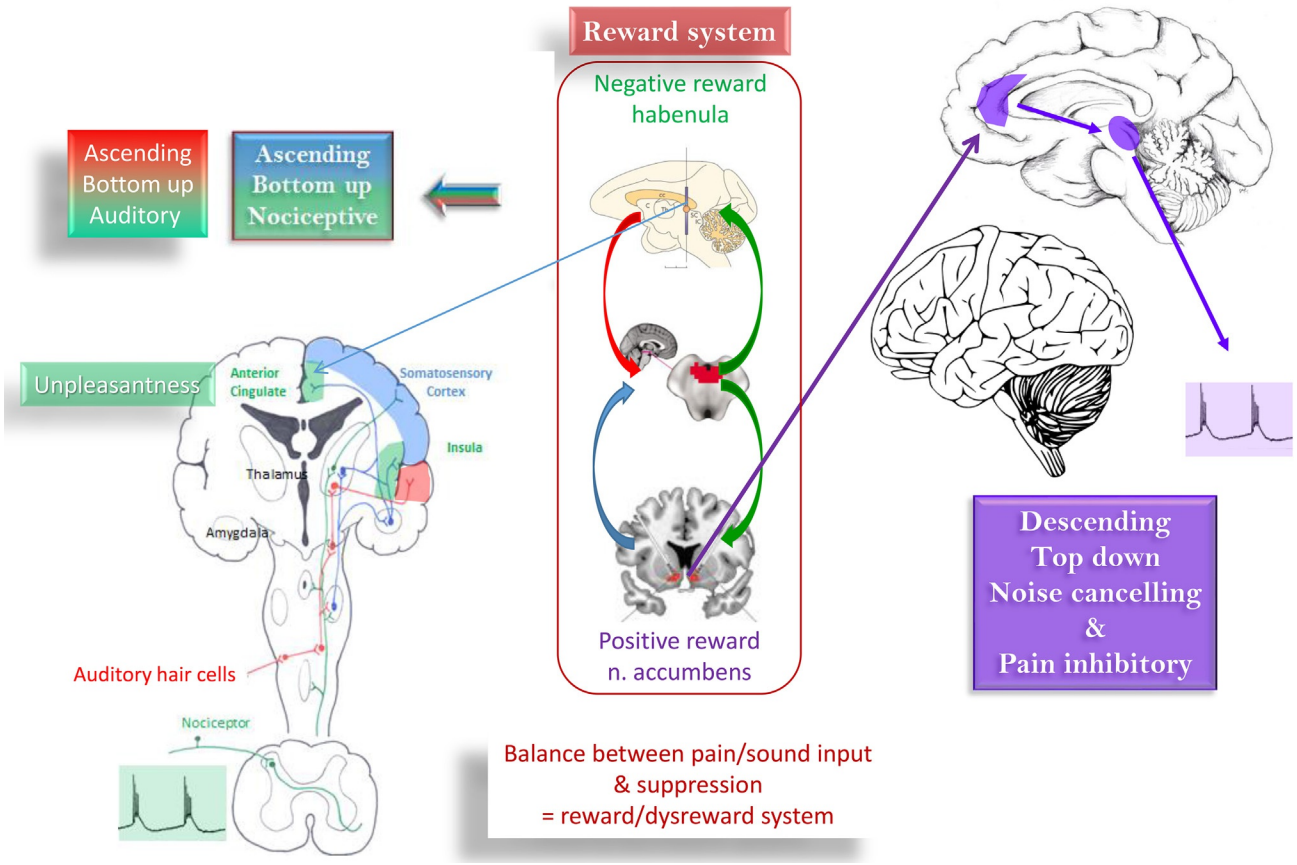

FIG. 5

Pain chronification is associated with increased structural and functional connectivity between the nucleus accumbens and the pregenual anterior cingulate cortex. The reward system can be simplified as a balance between positive (accumbens) and negative (habenula) reward, computed by the ventral tegmental area. Central panel: red arrow = glutamatergic, blue arrow = GABAergic and green arrow = dopaminergic.

Bayesian brain (De Ridder et al., 2014b; Donoso et al., 2014; Friston, 2010; Friston et al., 2006; Knill and Pouget, 2004; Kording, 2007), which is basically the predictive brain model with added updating via sensorimotor exploration of the environment (De Ridder et al., 2012a; Friston, 2010; Knill and Pouget, 2004). Bayesian inference can therefore be conceptualized as the use of sensorimotor and social information from the environment to update memory-based prior representations or models of the world (held before acquiring new inputs) to produce posterior representations (that emerge after acquiring those sensory or social inputs) and which integrate action-relevant information (Jackson, 1887).

Key to survival and procreation is our ability to rapidly attend to, identify, and learn from surprising events, i.e., prediction errors, to decide on present and future courses of action (Ranganath and Rainer, 2003).

Auditory or somatosensory deafferentation, which leads to sensory deprivation, limits the amount of information the brain can acquire to make sense of the world. In other words, it increases the uncertainty inherently present in the environment (De Ridder et al., 2014b,c). In order to decrease topographically selective uncertainty, the topographically deafferented brain area will look for the missing information or fill in the missing information. As wrongly predicted things are difficult to ignore, because it is crucial to experience them to update our understanding of the environment (Fletcher and Frith, 2009), this will increase the salience, the biological relevance, attached to the missing information (De Ridder et al., 2014b). This explains why somatosensory deprivation leads almost universally to phantom perception in 90–98% of limb amputees (Ramachandran and Hirstein, 1998). Phantom pain, a specific kind of phantom perception, is present in 70% of limb amputees (Sherman et al., 1984). Similarly, deprivation of auditory input can result in an auditory phantom phenomenon, also known as tinnitus. In sudden deafness 67% of patients present with tinnitus (Graham et al., 1978). In patients presenting with a vestibular schwannoma patients 70–80% of patients have tinnitus ipsilateral to the schwannoma (Moffat et al., 1998). In summary, in order to reduce the uncertainty associated with somatosensory or auditory deafferentation, the brain will fill in the missing information, either by retrieving the missing input from the cortical neighborhood or from memory, thereby generating tinnitus or somatosensory percepts, including pain (De Ridder et al., 2014b).

The Bayesian brain model has also been applied to tinnitus (De Ridder et al., 2014b,c; Durai et al., 2018, 2019; Hullfish et al., 2019; Lee et al., 2017; Sedley et al., 2016, 2019; Vanneste and De Ridder, 2016; Vanneste et al., 2019a). In essence, brains are prediction machines, essential in navigation/movement, using information from previous experiences (memory), to predict future events (intelligence), based on current context, in relation to the self, to reduce uncertainty, important for natural and sexual selection.

The brain can make multiple predictions in parallel (De Ridder et al., 2013; Donoso et al., 2014) and the prediction which best fits the sensory sampling survives and becomes the next percept (De Ridder et al., 2013). If in doubt, the percept will switch between predictions, as readily noted in the Rubin vase and the Necker cube

illusions. The reliability or precision of the current behavioral strategy is encoded by ventral medial prefrontal cortex and pregenual anterior cingulate cortex (Donoso et al., 2014), while the reliability of alternative behavioral strategies is encoded by lateral frontopolar cortex. When the reliability of the current strategy decreases, the behavioral strategy switches to the alternative. This switching is encoded by rostral to dorsal anterior cingulate cortex, and the rejection of the current strategy is encoded by ventrolateral prefrontal cortex, while the confirmation of new behavioral strategy as actor is encoded by ventral striatum, i.e., nucleus accumbens (Donoso et al., 2014). It is unsurprising that the neural correlates of this model partially overlap with reinforcement learning (Castronovo et al., 2016; Garrison et al., 2013; Glascher et al., 2010; Lee et al., 2014). Dopaminergic reinforcement learning in essence is a Bayesian mechanism (Friston et al., 2012; Gershman, 2015; Mathys et al., 2011), in which it is not the reward per se that reinforces behaviors but the difference between the predicted value of future rewards and their realized value (Montague et al., 1996; Schultz et al., 1997). And the prediction of the reward or punishment drives the dopaminergic synaptic gain or precision (Friston et al., 2012), permitting to select the most fitting prior belief or prediction.

Translating this to chronic pain, it can be proposed that in chronic pain the dorsal anterior cingulate cortex switches the current pain-free state to a painful state (via the habenula) when the reliability of the pain-free state decreases, switching to the alternative state, i.e., the painful state. This can occur when pain can be expected or predicted, especially in a stressful situation (Peters et al., 2017), which increases the reliability or precision of the prior belief (Peters et al., 2017). This can be easily understood, as in a stressful situation every stimulus may be behaviorally relevant, increasing synaptic gain. And indeed, most tortured people do develop chronic pain (Thomsen et al., 2000), and the development of chronic pain after surgery is best predicted by preoperative stress (McCowat et al., 2019). The accumbens confirms that it is beneficial for computing to use the painful state as the new reference state. The pregenual anterior cingulate cortex confirms the painful state as reliable and the functional connectivity between the nucleus accumbens and pregenual anterior cingulate cortex maintains the painful state. Indeed, chronification of acute to chronic pain involves the presence of both functional (Baliki et al., 2012) and structural connectivity (Mansour et al., 2013) between the nucleus accumbens and the pregenual anterior cingulate cortex (Baliki et al., 2012; Mansour et al., 2013). This concept can also be translated to chronic tinnitus. Deafferentation based spontaneous activity in the subcortical auditory pathway could constitute a “tinnitus precursor” which is normally ignored as imprecise, i.e., unreliable evidence against the reference of “silence” (Sedley et al., 2016). If precision (synaptic gain) rises sufficiently then tinnitus is perceived. Perpetuation arises through focused attention, which further increases the precision or reliability of the precursor, and resetting of the default prediction to expect tinnitus (Sedley et al., 2016). In chronic tinnitus, the dorsal anterior cingulate cortex switches the current tinnitus-free state to a tinnitus state (via the habenula). The accumbens confirms the tinnitus state as beneficial, i.e., as the new reference state. The pregenual anterior cingulate cortex confirms the tinnitus

state as reliable and the functional connectivity between the nucleus accumbens and pregenual anterior cingulate cortex maintains the tinnitus state. This can also explain the functional connectivity between the nucleus accumbens and the pregenual anterior cingulate cortex as well as the functional connectivity between the nucleus accumbens and the auditory cortex (Hullfish et al., 2018). In tinnitus patients with high distress, i.e., suffering, the connectivity extends to other areas and also involves connections between the habenula and dorsal anterior cingulate cortex, ventral tegmental area and parahippocampal area, nucleus accumbens and dorsal anterior cingulate cortex, and between the nucleus accumbens and parahippocampal area (Hullfish et al., 2018) incorporating both the contextual and the affective component of tinnitus in the reference state network.

6 Consequences of this Bayesian imbalance model

This model has some important implications: (1) It can be used to develop an objective measure for pain and tinnitus, using supervised machine learning, and (2) It can lead to some novel treatment approaches for tinnitus and pain. This model suggests that in order to find an objective measure for tinnitus and pain, a few regions of interest (ROIs) can be selected, consisting of hubs for the lateral, medial and inhibitory pathways, as well as the reward system. The hubs are the pregenual anterior cingulate cortex, rostral to dorsal anterior cingulate cortex, somatosensory cortex, auditory cortex, parahippocampus, accumbens and habenula. The functional and effective connectivity measures can be computed between these regions of interests, and especially between the nucleus accumbens and pregenual anterior cingulate cortex and the nucleus accumbens and the somatosensory cortex, auditory cortex and parahippocampus. These regions of interest can be used so that artificial intelligence under the form of (supervised) machine learning can detect patterns associated with painfulness or loudness, suffering, and the percentage of the time the pain or tinnitus is dominantly present. As such, an objective EEG measurement of global pain or tinnitus and their characteristics can be developed.

This heuristic pathophysiological furthermore permits to develop some novel treatments. This Bayesian approach suggests that the best treatment for tinnitus and pain may be via reconditioning, making use of either the positive reward (nucleus accumbens) or negative reward (habenula). This is basically a surgical but very targeted version of tinnitus retraining therapy (Jastreboff and Hazell, 2004; Jastreboff and Jastreboff, 2000).

Reconditioning stimulation is a novel concept based on the fact that it should theoretically be possible to recondition the brain through paired stimulation of external stimuli with electrical stimulation of the reward system, thereby rewarding certain stimuli and/or disrewarding other stimuli (De Ridder and Vanneste, 2016b). Chronic tinnitus and chronic pain can be regarded as a paradoxical behavioral relevance (salience) attached to the tinnitus sound or pain stimulus (De Ridder et al., 2011b), thereby preventing habituation to the phantom sound or pain, and

consequentially the pain and sound are maintained in consciousness because the symptom is considered behaviorally relevant (De Ridder et al., 2011b). This is in keeping with the fact for both pain (Boly et al., 2007) and sound (Sadaghiani et al., 2009), perception of the stimuli depends on the simultaneous co-activation of the salience network (dorsal anterior cingulate cortex and anterior insula) (Seeley et al., 2007). Thus, it has been proposed that by pairing the non-tinnitus frequencies to a rewarding stimulation in the nucleus accumbens the salience of the non-tinnitus sounds can be increased and by not rewarding the tinnitus-matched frequencies the relative salience of the tinnitus-matched frequencies can be decreased (De Ridder and Vanneste, 2016b). Furthermore, a disrewarding stimulation in the habenula paired to the tinnitus-matched frequency could also remove the salience of the tinnitus tone (De Ridder and Vanneste, 2016b). As such, a new reference resetting is enforced, reinstating another balance between the pregenual anterior cingulate cortex, rostral to dorsal anterior cingulate cortex and somatosensory/auditory cortex (parahippocampal area).

Alternatively, the imbalance can be addressed directly: the pregenual anterior cingulate cortex can be activated, e.g., through anodal stimulation, with simultaneous cathodal suppression of the somatosensory/auditory cortex/parahippocampus and rostral to dorsal anterior cingulate cortex. Or the pregenual anterior cingulate cortex can be uptrained, using neurofeedback, and the somatosensory/auditory cortex/parahippocampus can be down trained, also reinstating a more normal balance between these areas.

7 Conclusion

The current perspective proposes that pain and tinnitus are the result of an imbalance between pain/tinnitus provoking medial and lateral pathways and the descending pain/noise inhibitory pathways. The imbalance can be the result of increased activity in the two pain/tinnitus evoking pathways or a decrease in pain/noise inhibitory pathways or an increase in the two pain/tinnitus evoking pathways, more so than the pain/noise inhibitory pathways. Based on data from the pain field it is proposed that the main drive may be a deficiency of the inhibitory pathways through decreased inhibition from the rostral to dorsal anterior cingulate cortex. This imbalance is controlled by the reward system. Integrating the Bayesian brain in this model suggests that ultimately pain/tinnitus is the result of dorsal anterior cingulate cortex switching to the pain/tinnitus state (via the habenula) and confirmation of this pain/tinnitus state as beneficial, i.e., as the new reference. The pregenual anterior cingulate cortex confirms the pain/tinnitus state as reliable, and this is maintained by the functional between the accumbens and pregenual anterior cingulate cortex. This model suggests that surgically targeting the reward system for reconditioning (De Ridder and Vanneste, 2016b; Evans et al., 2015) may be a useful approach, which is compatible with the original neurophysiological model proposed for tinnitus (Jastreboff, 1990).

It permits also to develop an objective measurement for pain and tinnitus using supervised machine learning, as well as to develop other novel treatment approaches.

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