Pain and cognitive pain modulation in aging

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Pain in our aging society

Medical advances over the past decades have led to an ever-increasing life expectancy. The proportion of the 65+ age group in Luxembourg has grown by 4.4 percent in the last 35 years, and over the last 30 years, life expectancy in Luxembourg has increased by 9.9 years for men and 7.6 years for women (STATEC, 2016). However, increased life expectancy does not necessarily translate into improvements in health and wellbeing. Many older adults suffer from acute or chronic pain. Pain is reported by 73 percent of older people in the community (Brody & Kleban, 1983), and more than 50 percent of them experience chronic pain, which increases to more than 80 percent among nursing home residents (Helme & Gibson, 2001). In Luxembourg, a recent study in long-term care homes has found that almost 40 percent of residents were routinely treated with pain medication (Frisch et al., 2015). Older persons with chronic pain consider their health as poorer (Patel et al., 2013) and use more healthcare services than those without pain (Lavsky-Shulan et al., 1985).

Pain perception in older people

Despite the fact that pain is so common in older people, surprisingly little is known about how the process of aging influences pain perception. As we get older, our body and our brain in particular undergo many structural, functional and biochemical changes. Some studies have demonstrated, for example, that the density of pain receptors in the skin is decreased by the age of 60 years (Gibson & Farrell, 2004). Biochemical studies have documented a marked reduction in neurotransmitters involved in pain perception in the skin and spinal cord of older adults (Gibson & Farrell, 2004). Consequently, older age seems to be associated with changes in the experience of pain, including a slight increase in pain threshold and decrease in pain tolerance (Lautenbacher et al., 2017). However, other studies have found no influence of aging on pain thresholds, and the influence on pain stimuli above threshold has not been tested (Farrell, 2012).

Even less is known about how aging affects the processing of pain at the level of the brain. Very few studies to date have investigated cerebral processing of pain in older adults (Yezierski, 2012). This is even more surprising given that the brain shows significant and widespread age-related changes in structure (e.g. neuronal loss, shrinking of neurons and reduction of synapses), neurochemistry (e.g. decreased production of neurotransmitters and their receptors) and function (Fjell et al., 2009). This brain aging typically includes those areas involved in pain processing, such as the prefrontal cortex, somatosensory cortex, insula and thalamus (**see Figure 1**). Therefore, pain is likely to be experienced very differently in older than in young adults (Farrell, 2012). We are aware of only two studies on age-related changes in pain processing in the brain. The first study showed that older participants had smaller responses in the brain to pain than young participants, in several areas related to pain perception. Some of these areas were also smaller in volume

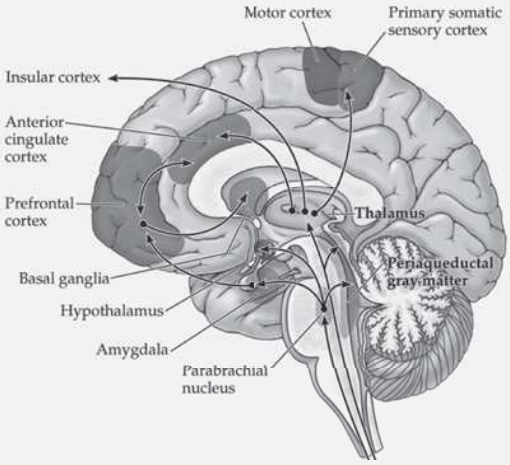

Figure 1.
Pain matrix

Schematic representation of brain areas that have consistently been shown to play a role in the processing of pain.

(Source: Martin, J.H. (2012). *Neuroanatomy Text and Atlas, Fourth Edition*. McGraw-Hill).

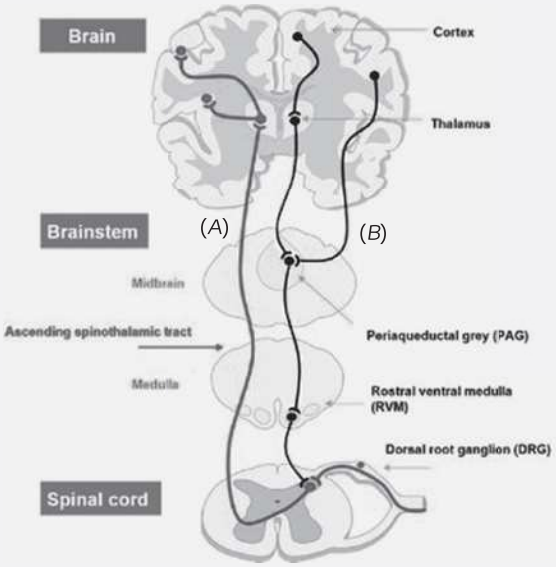

Figure 2.
Descending pain inhibition

Simplified depiction of the bottom-up pain processing pathway (*A*) and the top-down descending inhibitory pathway (*B*). Descending pain modulation project from areas in the cortex (e.g. the prefrontal cortex), via the periaqueductal gray in the brainstem down to the spinal cord. Here it can block the transmission of upcoming pain signals from the body (red pathway).

(Source: Cioffi, C. L. (2018). *Journal of Medicinal Chemistry 61*, 2652–2679).

in older than younger participants, leading the authors to conclude that the older adults had reduced processing capacity in these regions (Quiton et al., 2007). However, this study used a very small sample size (only 7 participants in each group) and the 'old' group contained participants from 56 years old, which is relatively young. A second study found that older adults showed less activity in some pain processing regions, which could not be accounted for by smaller volumes (Cole et al., 2010). Despite several methodological limitations in these studies, they do suggest that, indeed, the brains of older people seem to process pain differently than those of younger adults. However, much more research is needed to understand precisely how aging influences pain perception.

Cognitive modulation of pain

One aspect of pain perception that is particularly prone to age-related changes is cognitive modulation of pain. This refers to the observation that pain can be influenced by psychological factors through 'top-down' control (Legrain et al., 2012). For example, our experience of pain is strongly influenced by previously painful experiences, expectations, beliefs and emotions (Tracey, 2010; Van der Meulen et al., 2017a; Wiech et al., 2008). This interaction between pain and cognition has recently received a lot of attention, as clinicians expect a better understanding to aid in the treatment of pain (Seminowicz & Davis, 2007). Many studies have now demonstrated the properties, mechanisms and pathways of this psychological modulation of pain in healthy young adults. However, almost nothing is known about the effect of aging on psychological pain modulation. Again, this is rather surprising, given the great likelihood of aging affecting cognitive aspects of pain perception. As mentioned, age-related atrophy is particularly apparent in the prefrontal cortex (Fjell et al., 2009) which is heavily involved in the psychological modulation of pain (Van der Meulen et al., 2017b; Wiech et al., 2008). The prefrontal cortex (PFC) can activate so-called descending pain inhibition mechanisms. These are neural pathways from cortical regions of the brain, via an area called the periaqueductal gray (PAG) in the brainstem, down to the spinal cord (Gebhart, 2004) (**see Figure 2**). Neural

signalling in these pathways can stop pain signals from the body from being processed. Some studies have documented a general age-related decline in this descending inhibition system (Edwards et al., 2003), which confirms the possibility that psychological pain modulation by the PFC may be affected by aging. Since impaired pain modulation is a risk factor in the development of chronic pain (Yarnitsky et al., 2008), this may contribute to the frequency of chronic pain in older adults. It is thus very important that we better understand how cognitive modulation of pain is affected with advanced age.

A research project on the influence of aging on pain

In our laboratory at the University of Luxembourg, we are currently conducting a large-scale research project in which we investigate pain perception in older adults, using different neuroimaging methods. These methods allow us to explore the effects of aging on how pain is processed in the brain, and what the neural mechanisms of cognitive pain modulation are. We study cerebral processing of pain and psychological pain modulation in groups of younger (18-35 years) and older (60+ years) healthy volunteers. In particular, we study prefrontal cortex (PFC) functioning and its impact on the ability to cope with pain. We focus on two important forms of cognitive pain modulation, namely distraction and expectations. Here we will present some preliminary data from this project.

In a first study, we investigated how effective a distractive task is at reducing pain. Distraction is a powerful psychological mechanism to reduce pain and the impact of distraction on pain has been demonstrated in many studies (e.g. Johnson, 2005). The analgesic effects of distraction result from a competition for attentional and emotional resources (Eccleston & Crombez, 1999). Pain demands attention and can thus be modulated when simultaneously engaging in another activity. Focusing attention is an important function of the PFC. Because of its reliance on the PFC, we would expect distraction to be less efficient at reducing pain in older adults. Due to PFC atrophy and weakened attentional resources, older adults may be less able to focus on the distraction task and ignore attention-demanding pain. There is substantial evidence for impaired attentional functioning with aging, with older adults showing larger interference effects and a reduced ability to focus on relevant tasks and being less able to ignore distractors (Kramer & Kray, 2006). However, no previous studies have directly investigated the analgesic effect of distraction, and its neural correlates, in older adults.

We present here some results from a subset (25 young and 25 older healthy adults) of the total group that took part in this study. Young participants were recruited through advertisements around the university campus and through word-of-mouth. The older adults were recruited with the support of the Cellule de Recherche of RBS – Center fir Altersfroen who published a call for participation in their magazine 'Aktiv am Liewen' and advertised the study on their premises. Ethical approval was granted by the national ethics committee (CNER) and the University's local ethics board. The participants were first invited to our laboratory where we assessed their attentional and other cognitive skills. After that they were invited to the ZithaKlinik (Hôpitaux Robert Schuman) where we studied their brain activity during a pain distraction paradigm. We used functional magnetic resonance imaging (fMRI) to investigate the degree of activation in the brain during the perception of pain with and without distraction. FMRI is a non-invasive technique using a strong magnetic field and radiofrequency pulses (**see Figure 3**).

This technique can visualise which regions of the brain receive more blood and are thus more active. The distraction task was a working memory task during which participants had to try and remember a series of letters while comparing these to letters presented previously. In a control condition, the task was a very easy letter detection task demanding minimal attention. Pain stimuli were delivered to the participants' forearms using a contact thermal stimulator: a small metal surface that can be rapidly heated up and cooled down, controlled by a computer (**see Figure 4**). After every pain stimulus, participants moved a cursor along a rating scale on a computer monitor using a handheld button box to indicate how painful it was for them.

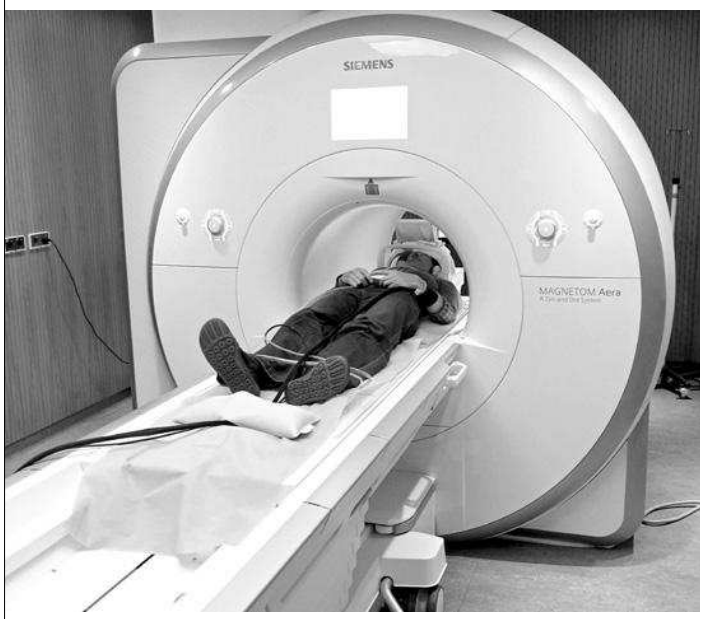

Figure 3.
Functional magnetic resonance imaging

Participants lie in an MRI scanner which generates functional images of the brain while participants receive painful heat stimuli during a distraction and a control condition.

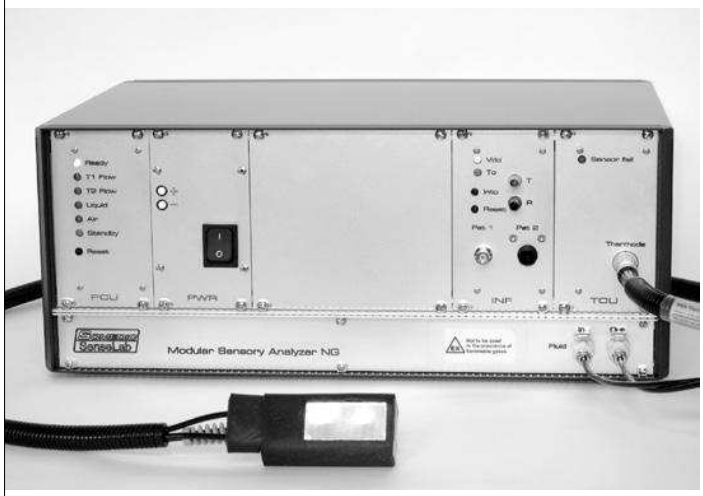

Figure 4.
Contact thermal stimulator

The device used to deliver painful heat stimuli to the arm of participants. (Source: Somedic, Sweden. Website: http://somedic.com/en/).

Smaller reduction in pain-related activation

The first results from this study show that, at a behavioural level, both participant groups showed a distraction effect: younger and older adults evaluated the thermal stimuli as significantly less painful during the difficult distraction task than in the control condition. There was no significant difference between the groups in these subjective ratings. When we look at the brain, older participants seemed to recruit a smaller network of brain areas related to pain perception, but the group difference was, again, not significant. However, things become interesting when we look at the 'neural distraction effect', or the reduction in pain-related brain activation during distraction.

The young participants showed a very clear neural distraction effect; there was a significant reduction in activation in some regions crucial for pain perception, namely the right anterior and posterior insula and somatosensory cortex (**see Figure 1**). The pain stimuli were administered to the participants' left arms, explaining the right-sided activation pattern (sensations from the body are processed in the opposite hemisphere of the brain). The somatosensory cortex is the area in the brain where sensory characteristics of events are coded, such as localisation and discrimination of pain intensity (Bushnell et al., 1999). The insula plays an important role in integrating cognitive information to modulate connected brain areas involved in the processing of sensory, emotional and cognitive components of pain perception (Starr et al., 2009). Additionally, the posterior insula specifically encodes the intensity of pain (Segerdahl et al., 2015). These regions constitute two of the main parts of the so-called 'pain matrix', a network of areas consistently activated in response to pain (Tracey & Mantyh, 2007) (**see Figure 1**).

The observation that these areas were less active in response to pain during the distraction task in the young participants matches the change in subjective pain ratings reported and suggests that there was indeed decreased processing of pain in the brain, due to the distraction. In the older group of participants, however, the neural distraction effect was much smaller. In fact, they did not show a reduction in activation due to distraction in any regions within the pain

matrix. In a direct group comparison, the neural distraction effect indeed appears significantly stronger in the young than in the older participants in several regions, including the right anterior and posterior insula, left posterior insula, the left posterior cingulate cortex and the left thalamus (**see Figure 5**). These latter two regions are also part of the pain matrix and play a role in the emotional reaction to pain (e.g. Nielsen et al., 2004) and localisation of pain (e.g. Bingel et al., 2003) respectively.

Less efficient top-down control of pain

The smaller reduction in activation in pain regions in the brains of older than of younger participants is very interesting and suggests that distraction is indeed less efficient in older persons. In addition, our fMRI data allow us to explore which brain areas were *more* activated during the distraction condition than during the control condition and to compare this between our two age groups. Looking at which areas were *more* active during distraction than during control shows us regions in the brain related to the neural mechanism of distraction. Distraction is a type of cognitive modulation of pain that depends on the functioning of the prefrontal cortex (PFC) which can activate descending control pathways, which in turn may then lead to an inhibition of the processing of upcoming pain signals. In the young participant group, we indeed find an increase in activation in the superior medial frontal gyrus during distraction from pain. In the older participant group, there is an absence of such prefrontal activation.

When directly comparing the distraction-related increase in activation between groups, we not only found a region in the PFC, but also in the periaqueductal gray (PAG) area in the brainstem. This latter area has a strong involvement in the descending pain control pathway responsible for the cognitive modulation of pain. Again, these results suggest that the mechanism for distraction (i.e. descending pain inhibition) is functioning less well in older than in younger participants.

Studying the role of expectations using electro-encephalography (EEG)

A second study within this research project focuses on the influence of expectations on pain. Expectations can shape our perception of pain to a large degree (e.g. Wager et al., 2004). For example, when we expect something to be minimally painful or when we expect a certain medical treatment to work, the pain we experience will be strongly attenuated. Again, the mechanism responsible for this type of pain modulation is through the descending pain control system (e.g. Eippert et al., 2009). In this study, which is ongoing at the time of writing, we specifically investigate the influence of aging on the way expectations can modulate our pain experience. This has, to the best of our knowledge, never been studied before. Our hypotheses are the same as for the distraction study, namely that PFC-mediated inhibition of pain is less efficient in older than in younger participants. Older participants would therefore show a less strong modulation of pain through expectations than young. Results from this study would confirm and strengthen the conclusions from the first study. Another addition of this study is that, this time, we are using a different neuroimaging technique, namely electro-encephalography (EEG). This method allows us to study the electrical activity of the brain by placing special sensors (electrodes) on the scalp surface (**see Figure 6**).

This is, again, a non-invasive technique that is used routinely in both clinic and research. Other than with fMRI, which allows us to visualise very precisely *where* in the brain processes take place, EEG has the advantage of having a very high temporal resolution. EEG allows us to study exactly *when* processes take place, with a precision in the order of milliseconds. We expect to see changes in the EEG data that mirror behavioural results of less reduction in pain in the older adults. By combining both neuroimaging methods, fMRI and EEG, we will be able to paint a complete picture of when and where changes occur during pain processing in our brains as we get older.

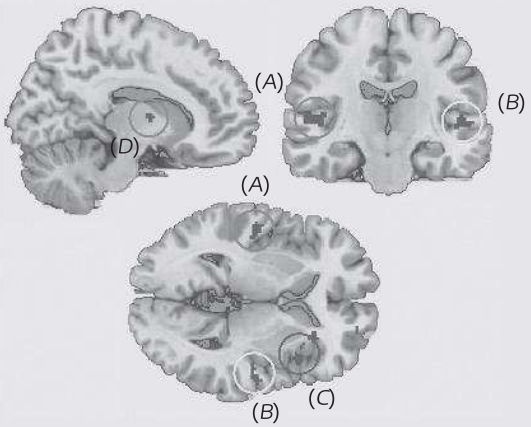

Figure 5.
Neural distraction effect

The red activated brain areas represent regions where young participants showed a significantly stronger neural distraction effect than older participants.

The neural distraction effect refers to a decrease in pain-related brain activity during distraction.

The present areas are all essential parts of the pain matrix, including the left posterior insula (*A*), right posterior insula (*B*), right anterior insula (*C*) and thalamus (*D*).

Figure 6.
The EEG cap

The cap with sensors used for electroencephalography recording.

Conclusion

We have presented here some first results from a large-scale research project on how pain processing changes as we get older. Pain in our aging population is a serious issue in society which urgently needs attention. Better understanding how aging influences basic processing of pain is a necessary first step towards developing more efficient interventions and management strategies, specifically targeted at the special needs of older people. So far, our results demonstrate clear age-related differences in the processing of pain on the neural level, even if on the behavioural level there do not seem to be large differences. In particular, we have shown that older adults benefit less from a distraction paradigm; they show much less pronounced reduction in pain-related processing in the brain than younger adults. This was paired with less activation in the system responsible for descending inhibition of pain, which underlies cognitive modulation of pain. These results already point to some very important changes that may take place with aging and might have far-reaching consequences for how we treat pain in our aging population. If older persons are indeed less able to modulate pain using the body's own pain inhibition system, we may have to revise our therapeutic approach for pain in older adults. For example, we would have to consider increasing drug dose or focusing on alternative treatment strategies to compensate for the loss of endogenous pain control.

Our results also point to a possible mechanism for the increased vulnerability of older persons to develop chronic pain (Farrell, 2012; Yarnitsky et al., 2008). Chronic pain conditions have indeed been associated with impairment of the descending pain control system (e.g. Ossipov et al., 2014). More research should focus on exploring how we could target this system specifically, using pharmacological or psychological approaches. Our project is the first to systematically explore cerebral pain processing and cognitive pain modulation in advanced age, and these first promising results encourage the continuation of this line of research.

Glossary

Acute pain
Pain which is of short duration and directly related to tissue damage.

Analgesic effect
Pain relieving effect.

Atrophy
Physiological process of breakdown of biological tissue.

Chronic pain
Pain that lasts at least 12 weeks and is not necessarily related to tissue damage.

Contact thermal stimulator
Computer-controlled device which allows rapid heating and cooling of a 25x50mm metal surface that is placed on the skin (see Figure 4).

Descending pain inhibition
Also called *endogenous pain control*. A neural pathway for the top-down control of pain, descending from the periaqueductal gray in the brainstem into the spinal cord (see Figure 2). This system can be triggered by cognitive states, through connections with cortical brain regions including the prefrontal cortex. Activating the system involves the release of neurotransmitters (opioids) that can block pain signals.

EEG
Electro-encephalography. A non-invasive *neuroimaging method* to record electrical activity of the brain, using small sensors (surface electrodes) on the scalp (see Figure 6). EEG enables us to study the exact time-course of the brain's reaction to pain.

fMRI
Functional magnetic resonance imaging. A non-invasive *neuroimaging method* using an MRI scanner to visualise brain activity. An active area of the brain increases the blood flow to this area, which changes the intensity of the signal measured by the MRI machine. This method allows us to determine with high precision which areas of the brain are involved in the perception of pain (see Figure 3).

Neuroimaging methods
Techniques used to visualize the structure and function of the nervous system, in particular the brain. Functional neuroimaging enables the visualization of the processing of information in the brain.

Neurotransmitter
A chemical messenger in our body which can transmit a signal from one neuron to another neuron, muscle or gland.

PAG
Periaqueductal gray. A nucleus in the brainstem (see Figure 1) which plays a crucial role in *descending pain inhibition* (see Figure 2). Stimulation of this area blocks the transmission of pain signals from the body to the brain and thus suppresses pain.

Pain threshold
The lowest intensity at which a stimulus is perceived as painful.

Pain tolerance
The maximum level of pain that a person is able to tolerate.

PFC
Prefrontal cortex. The cortex covering the front part of the frontal lobe (see Figure 1). This brain region mediates higher cognitive functions such as attention, decision-making and regulating behavior and emotions.

Synapse
The gap between two neurons across which an electrical or chemical signal can be passed on.

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