Neurobiology of Learning and Memory 123 (2015) 92–99

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Sex differences in cerebellar mechanisms involved in pain-related safety learning

Franziska Labrenz [a], Adriane Icenhour [a], Markus Thürling [b], Marc Schlamann [c], Michael Forsting [c], Dagmar Timmann [b], Sigrid Elsenbruch [a,*]

[a] Institute of Medical Psychology and Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, Germany
[b] Department of Neurology, University Hospital Essen, University of Duisburg-Essen, Germany
[c] Institute of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, University of Duisburg-Essen, Germany

ARTICLE INFO

Article history:
Received 20 January 2015
Revised 20 April 2015
Accepted 15 May 2015
Available online 21 May 2015

Keywords:
Cerebellum
Visceral pain
Safety learning
Conditioning

ABSTRACT

Recent studies have suggested that the cerebellum contributes to the central processing of pain, including pain-related learning and memory processes. As a complex experience with multiple emotional and cognitive facets, the response to pain and its underlying neural correlates differ between men and women. However, it remains poorly understood whether and to what extent sex differences exist in the cerebellar contribution to pain-related associative learning processes. In the present conditioning study with experimental abdominal pain as unconditioned stimuli (US), we assessed sex-dependent differences in behavioral and neural responses to conditioned warning and safety cues in healthy volunteers. The results revealed that in response to visual stimuli signaling safety from abdominal pain (CS^-), women showed enhanced cerebellar activation in lobules I–IV, V, VI, VIIIa, IX and X as well as Crus II and the dentate nucleus, which are mostly representative of somatomotor networks. On the other hand, men showed enhanced neural activation in lobules I–IV, VI, VIIb, VIIIb, IX as well as Crus I and II in response to CS^-, which are representative of frontoparietal and ventral attention networks. No sex differences were observed in response to pain-predictive warning signals (CS^+). Similarly, men and women did not differ in behavioral measures of conditioning, including conditioned changes in CS valence and contingency awareness. Together, we could demonstrate that the cerebellum is involved in associative learning processes of conditioned anticipatory safety from pain and mediates sex differences in the underlying neural processes. Given the high prevalence of chronic pain conditions in women, these results may contribute to improve our understanding of the acquisition and manifestation of chronic abdominal pain syndromes.

© 2015 Elsevier Inc. All rights reserved.

1. Introduction

The cerebellum has long been considered to be mainly involved in motor control and the integration of sensory and motor information. Recently, however, experimental studies challenged this view by constituting a topographic organization of the human cerebellum also for non-motor functions including cognitive and emotion processing (Buckner, 2013; Koziol et al., 2014; Stoodley & Schmahmann, 2009; Strick, Dum, & Fiez, 2009; Timmann et al., 2010). These functional contributions are not assumed to have a primary localization, but similar to its role in motor control, the cerebellum is thought to modulate processing in cortical and subcortical brain structures (Bellebaum & Daum, 2011; Freeman, 2014). This supportive function is carried out through interconnections forming multiple closed-loop cerebro-cerebellar circuits through which information primarily from frontal and parietal lobes are conveyed to the cerebellum and then back to cortical areas (Buckner, Krienen, Castellanos, Diaz, & Yeo, 2011; Krienen & Buckner, 2009; O'Reilly et al., 2010; Salmi et al., 2010). Parts of these connections likely play a role in the central processing of pain, including pain-related associative learning and memory processes. Regarding the latter, several animal and human studies report that the cerebellum is associated with emotional, cognitive and motor associative learning in the context of classical conditioning (Timmann et al., 2010).

However, little is known about the contribution of cerebellar regions to the central processing of pain and its anticipatory

* Corresponding author at: Institute of Medical Psychology & Behavioral Immunobiology, University Hospital Essen, University of Duisburg-Essen, Hufelandstr. 55, 45147 Essen, Germany. Fax: +49 201 723 5948.
E-mail address: sigrid.elsenbruch@uk-essen.de (S. Elsenbruch).

http://dx.doi.org/10.1016/j.nlm.2015.05.006
1074-7427/© 2015 Elsevier Inc. All rights reserved.

modulation (Bushnell, Ceko, & Low, 2013; Wiech, Ploner, & Tracey, 2008). There is some evidence documenting that the cerebellum supports the processing of experimental pain with its complex sensory, emotional and neuro-cognitive facets in healthy subjects (Helmchen, Mohr, Erdmann, Petersen, & Nitschke, 2003; Moulton, Schmahmann, Becerra, & Borsook, 2010; Moulton et al., 2011), in patients with chronic pain conditions (Borsook, Erpelding, & Becerra, 2013; Rosenberger et al., 2013) as well as in patients with cerebellar disease (Ruscheweyh et al., 2014). Our line of conditioning research in the visceral pain field aims at elucidating neuro-cognitive aspects in the pathophysiology of chronic abdominal pain such as in irritable bowel syndrome (IBS) (Elsenbruch, 2011). We have characterized the cortical and subcortical (Gramsch et al., 2014; Icenhour et al., 2015; Kattoor et al., 2013) as well as cerebellar regions (Kattoor et al., 2014) involved in anticipatory pain-related fear using experimental abdominal pain as unconditioned stimuli (US) and visual cues as conditioned stimuli (CS). While the majority of these reports were based on mixed samples of men and women, we most recently documented sex differences in the neural mechanisms mediating pain-related learning and its extinction (Benson et al., 2014). Here, we could present sex-related differential neural activation at cortical sites within the insula and posterior parietal cortex, both regions known to be important in interoception, multi-modal integration of sensory input as well as inhibitory learning. However, recent studies also found evidence for sex differences within the fear circuit comprised of the amygdala, hippocampus, prefrontal and cingulate cortex, although most of these studies include stress as an additional sex-specific modulator of fear conditioning (Farrell, Sengelaub, & Wellman, 2013; Lebron-Milad et al., 2012; Merz et al., 2013). These initial results, which did not focus on the cerebellum, are highly interesting given the well-established female preponderance of chronic pain (Chang et al., 2006, Mogil, 2012) including IBS (Lovell & Ford, 2012), and a growing body of evidence supporting sex differences in the central processing of various types of aversive stimuli, including pain (Fillingim, King, Ribeiro-Dasilva, Rahim-Williams, & Riley, 2009; Hashmi & Davis, 2014) and in the context of various psychiatric disorders (Altemus, Sarvaiya, & Epperson, 2014; Bangasser & Valentino, 2014).

Within the cerebellum, sex differences in the response to aversive stimuli have rarely been addressed. So far, studies reported sex differences either with a focus on connected areas, e.g. in connectivity between the periaqueductal gray and cerebellum (Linnman, Beucke, Jensen, Gollub, & Kong, 2012) or with a focus on whole brain data reporting differential neural activation in the cerebellum only as a secondary finding (Berman et al., 2000; Kano et al., 2013). Therefore, herein our goal was to identify sexually dimorphic areas in the human cerebellum that contribute differently to the associative learning of pain-related warning and safety signals (i.e., CS^+ and CS^-, respectively). To do so, we reanalyzed the acquisition phase of an existing dataset (Icenhour et al., Hum Brain Mapp, in press) from a large conditioning study conducted in a mixed sample of healthy men and women using more elaborate and advanced analyzing methods. Based on our earlier findings (Benson et al., 2014), we expected sex differences during the acquisition of conditioned pain-related warning signals (CS^+). Particularly, we assumed that women would show enhanced neural activation in cerebellar regions associated with emotional processing whereas we expected men to show enhanced neural activation in regions associated with cognitive processing. In addition, we aimed to explore sex differences in response to conditioned safety signals (CS^-) since our findings in a sample of IBS patients consisting primarily of women revealed a specific relevance of non-pain predictive conditioned stimuli (CS^-) in IBS (Icenhour et al., 2015).

2. Methods

2.1. Participants

The present report constitutes a reanalysis of acquisition phase data from forty-eight healthy volunteers (24 men and 24 women) who were recruited for a study on extinction learning which does not address effects of participants' sex (Icenhour et al., Hum Brain Mapp, in press). Subjects were excluded from participation if they were outside the age range of 18–60 years or had a body mass index (BMI) outside the range of 18–30, reported any concurrent medical condition, anal tissue damage (e.g., painful hemorrhoids) or a history of psychological/psychiatric conditions (based on self-report) or scores above the published cut-offs (i.e., $\geqslant 8$) for mild-to-moderate symptoms of depression and/or anxiety, respectively, on the Hospital Anxiety and Depression Scale (HADS) (Herrmann-Lingen, Buss, & Snaith, 2005). Additional exclusion critera were any evidence of structural brain abnormality upon structural MRI scan, or if subjects met any of the usual MRI-specific exclusion criteria (i.e., phobic anxiety, claustrophobia, ferromagnetic implantations). To control for any functional or organic gastrointestinal conditions, frequency and severity of several symptoms were ruled out with a standardized in-house questionnaire (Lacourt et al., 2013) and personal interview. Participants were additionally characterized with respect to chronic stress (Trier Inventory for Chronic Stress, TICS, screening scale; Schulz, Schlotz, & Becker, 2004) and personality traits (NEO-FFI, Borkenau & Ostendorf, 2008). We included 17 women on hormonal contraceptives and 7 naturally-cycling women but did not control for confounding effects of the menstrual cycle. Additionally, pregnancy was routinely excluded with a commercially available urinary test on the day of the study. The study protocol was approved by the local ethics committee (University Hospital Essen, University of Duisburg-Essen, Germany). All participants gave written informed consent and were reimbursed for their participation. With respect to the instruction of participants, they were informed that the goal of the study was to address neural correlates underlying visceral pain-related learning and memory processes in the context of visceral pain and IBS.

With respect to sample characteristics, the 24 women (mean age ± SD: 32.1 ± 13.6 years) and 24 men (27.6 ± 6.7 years) were all of normal weight and BMI did not differ significantly between women (23.62 ± 5.91) and men (24.22 ± 2.70) ($t_{(46)} < 1$, $p = .651$). Women scored higher on the TICS screening scale (13.92 ± 8.00) when compared to men (9.04 ± 6.20) ($t_{(46)} = -2.359$, $p = .023$), indicating greater chronic stress. Likewise, women (15.37 ± 3.59) scored significantly higher on the neuroticism subscale of the NEO-FFI than men (12.94 ± 3.02) ($t_{(35)} = -2.215$, $p = .033$) although questionnaire data were missing from 11 participants (5 female and 6 male). For anxiety and depression, none of the participants reached clinically-relevant HADS scores as per exclusion criteria, although women scored significantly higher on anxiety (mean score ± SD for women: 4.04 ± 2.33; for men: 1.83 ± 1.86; $t_{(46)} = -3.630$, $p = .001$) but not depression (women: 1.42 ± 1.53; men: 1.29 ± 1.52; $t_{(46)} = -.284$, $p = .778$). Assessment of sensory and rectal pain thresholds revealed comparable pressures for first perception (mean pressure ± SD for women: 12.17 ± 3.44 mmHg; for men: 13.42 ± 3.56 mmHg; $t_{(46)} = 1.238$, $p = .222$), but lower thresholds for pain in women (28.58 ± 11.58 mmHg) compared to men (35.04 ± 10.30 mmHg) ($t_{(46)} = 2.042$, $p = .047$), supporting the need to utilize individualized pain intensities for US application during conditioning.

2.2. Study design

The basic study design and conditioning protocol have previously been described in detail (Kattoor et al., 2013). The study this

Download English Version:

https://daneshyari.com/en/article/936451

Download Persian Version:

https://daneshyari.com/article/936451

Daneshyari.com