CHEMOSENSATION IN ANXIETY: THE TRIGEMINAL SYSTEM MATTERS

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ABSTRACT

The presence of a perceptual bias due to anxiety is well demonstrated in cognitive and sensory task for the visual and auditory modality. Event-related potentials, by their specific measurement of neural processes, have strongly contributed to this evidence. There is still no consensus as to whether such a bias exists in the chemical senses; chemosensory event-related potentials (CSERP) are an excellent tool to clarify the heterogeneous results, especially since the Late Positive Component (LPC) may be an indicator of emotional involvement after chemosensory stimulation. This research examined the association between state and trait anxiety and the amplitude and latency of pure olfactory and mixed olfactory-trigeminal LPC. In this study, 20 healthy participants (11 women) with a mean age of 24.6 years (SD=2.6) completed a validated questionnaire to measure anxiety (STAI), and CSERP were recorded during 40 pure olfactory stimulations (phenyl ethanol) and 40 mixed olfactory-trigeminal stimulations (eucalyptol). LPC latency and amplitude were measured at Cz (electrode located at midline central) for each participant. We observed a significant negative correlation between LPC latencies and the state anxiety scores for the mixed olfactory-trigeminal condition ($r(18) = -.513$; $p = .021$), but not for the pure olfactory condition. We did not observe any effect on LPC amplitudes. This study suggests that a higher level of state anxiety is related to a more rapid perceptual electrophysiological response for mixed olfactory-trigeminal stimuli but not for pure odors.

INTRODUCTION

Whether anxiety stems from a disorder, such as generalized anxiety disorder, or whether it is non-pathological, it can affect sensory and cognitive domains (Robinson et al., 2013). Anxiety can be beneficial or detrimental to performance; this distinction depends mainly on the level of anxiety experienced, the nature of the task and its degree of difficulty (Arent & Landers, 2003; Eysenck & Calvo, 1992). Many studies have investigated the impact of anxiety on visual or auditory processing (Asutay & Västfjäll, 2015; Bar-Haim et al., 2007; Peschard et al., 2014). These studies suggest an increased selective attention to possible threats, manifested by a shorter reaction time to ambiguous or threatening stimuli compared to a longer reaction time to neutral stimuli in the presence of threatening stimuli (Eldar et al., 2010; Frewen et al., 2008). Compared to vision and audition, less is known about the influence of anxiety on chemosensory processing. This is surprising considering that, unlike other senses, olfactory information processing takes place, at least partly, in the limbic system, which includes areas of basic emotion (Kadohisa, 2013; Kontaris et al., 2020). Indeed, the olfactory bulb has direct and unique connections with the amygdala and the hippocampus. These structures are part of the primary olfactory cortex and have strong reciprocal connections with the orbitofrontal cortex. This circuit is strongly involved in the processing and regulation of emotions and particularly in responses to threatening environmental stimuli. (Shipley & Ennis., 1996; Benarroch, 2010; Soudry et al., 2011)

For instance, individuals with high levels of state anxiety had (1) increased accuracy in discriminating negative odors, (2) hypersensitivity of the primary olfactory cortex to negative odors and (3) an intensified skin conductance response for negative odors (Krusemark & Li, 2012). The authors suggest an exaggerated processing of olfactory threats (eg., trimethylamine - rotten fish smell) in anxiety for behavioral, autonomic physiological, and neural domains. In a second functional imaging study, after anxiety was experimentally induced, neutral odors became negative. This change in affective perception was related to the level of induced anxiety. The orbitofrontal cortex as well as the amygdala showed an increased response to neutral odors after anxiety induction (Krusemark et al., 2013). When intensity and detection time following pleasant, neutral, and unpleasant odor stimuli were assessed, both pleasant and unpleasant odors were perceived more quickly and as more intense than neutral stimulus for individuals with high levels of trait anxiety (Chen & Dalton, 2005). Similarly, participants with high trait anxiety had faster reaction times to pleasant and unpleasant olfactory stimuli when compared with their counterparts with low trait anxiety levels. Further, trait anxiety was negatively correlated with reaction time (La Buissonnière-Ariza et al., 2013). However, although several studies suggest an increase of olfactory detection abilities in individuals with high levels of anxiety, other studies suggest that it may actually be reduced (Takahashi et al., 2015; Pollatos et al., 2007; Clepce et al., 2012; Krusemark et al., 2013). These inconsistences between studies could be due to differences in sample characteristics and olfactory testing methods (e.g., the type and nature of odors used), as these can have a significant impact on olfactory processing (Doty et al., 1997). The presence of a perceptual bias similar to that identified for auditory and visual perception remains to be confirmed for chemical senses.

When we smell something, it usually activates more than our olfactory system. In fact, the trigeminal system is a third chemical sense adjacent to smell and taste (Gerhold &

Bautista, 2009). The trigeminal system allows for the perception of the spiciness of hot peppers or the freshness of peppermint (Filiou et al, 2014; Viana, 2011). The trigeminal system is independent from the olfactory system, i.e., it has (1) distinct chemoreceptors (e.g., TRPM8, TRPV1; Gerhold & Bautista, 2009), (2) distinct conveying structures (i.e., the trigeminal nerve) and (3) distinct central nervous processing centers (Friedland & Harteneck, 2017; Brand, 2006). However, the trigeminal system interacts very closely with the olfactory system as most odorous substances activate both the olfactory and the trigeminal system (Doty et al., 1978; Filiou et al., 2014; Frasnelli et al., 2011; Wysocki et al., 2003), especially in higher concentrations. Such stimuli are called mixed olfactory-trigeminal stimuli as opposed to pure odorants that only activate the olfactory system (Tremblay et Frasnelli, 2018). The trigeminal system plays a role in protecting the body from environmental threats (Gerhold & Bautista, 2009). Activation of the trigeminal system may induce reflexes such as sneezing or coughing which protect the integrity of the airways (Baraniuk & Kim, 2007; Pfaar et al., 2009).

In regards of anxiety, people suffering from post-traumatic stress show increased sensitivity to trigeminal stimuli (Cortese et al., 2018; Croy et al., 2010). Trigeminal detection sensitivity has also been found to be related to enhanced neuroticism and induced stress (Croy et al., 2011; Pacharra et al., 2016). As mentioned above, these findings are not surprising given the protective role of the trigeminal system. In fact, all the aforementioned studies that investigated the association between anxiety and olfactory processing used stimuli that may have activated the trigeminal system, at least to some extent. In order to examine the link between anxiety and chemosensory processing it is therefore necessary to distinguish between pure olfactory and mixed olfactory-trigeminal stimuli while using odorants of similar valence.

From a methodological point of view, most previous studies used behavioral measures as dependent variables. This can be problematic because they rely on anxiety-sensitive cognitive functions, such as working memory, making it impossible to properly isolate how anxiety influences olfaction (Moran et al., 2016; Hedner et al., 2010) One potential approach to reducing this bias would be to use Chemosensory Event-Related Potentials (CSERP), a technique that uses electroencephalography to record specific components of brain activity in response to specific events or stimuli (Blackwood & Muir, 1990). Event-related potentials (ERP) studies have supported the notion of a perceptual bias of anxiety for vision and audition (Carlson, 2021). CSERPs have been reported to be reliable and as valid as visual and auditory ERPs (Thesen & Murphy, 2002). Some previous studies using ERPs and assessing cross-modality between olfaction and vision have shown the important influence of olfaction on visual judgment task and categorization tasks. These studies argue that olfaction plays an important role, even beyond vision, in the perception of threats and incongruent cues (Bensafi et al., 2002; Demattè et al., 2007; Hörberg, 2020). However, to our knowledge, the link between olfactory perception and anxiety has never been explored using CSERPs.

In the visual and auditory modality, the P300 component is the prime parameter to study the impact of anxiety on perception. Some studies evaluating the characteristic of this component in patients with anxiety disorder show a shorter latency and a greater amplitude during oddball protocols (Reeb-Sutherland et al., 2009; Hanatani et al., 2005; Enoch et al., 2001.) In the olfactory modality, the P300 component analogue is the Late

Positive Component (LPC), an endogenous component of brain activity (Cortese et al., 2018; Ioakeimidis et al., 2021; Sur & Sinha, 2009). The LPC usually reaches its full amplitude at the parieto-central region and is generally observed 400-900ms after stimulation (Andersson et al., 2018; Ohla & Lundström, 2013). Sex differences are reported for the LPC following a trigeminal stimulation (CO_2). Amplitude tends to be greater in women than in men (Ohla & Lundström, 2013).

The measurement of the LPC is known as valid measure of attentional allocation and more precisely as an indicator of emotional engagement (Andersson et al., 2018; Invitto et al., 2018; Pause & Krauel, 2000; Pause et al., 1996; Singh et al., 2019). Furthermore, it is suggested that the pleasantness/unpleasantness aspect of odors modulate the amplitude of the LPC, where the amplitude is greater for unpleasant odors (Lundström et al., 2006). Therefore, the LPC may be a component that is highly susceptible to be affected by anxiety.

In this study, we aimed to determine whether there is an association between anxiety and the LPC after pure olfactory and mixed olfactory-trigeminal stimulations. We hypothesized (1) that the level of anxiety will be correlated with the latency of the LPC for mixed olfactory-trigeminal stimulation but not for pure olfactory stimulation; (2) that the level of anxiety will be correlated with the amplitude of the LPC for mixed olfactory-trigeminal stimulation but not for pure olfactory stimulation.

METHODS

PARTICIPANTS

A total of 31 healthy participants (18 women) aged between 21 and 30 years (mean age 24.6 years, standard deviation [SD] = 2.5 years) participated in this study. Eleven participants were excluded from the EEG analysis due to artifacts in the EEG signal (see "EEG processing"). Therefore, 20 participants (11 women, mean age = 24.6, [SD] = 2.6) remained in the analysis. We recruited participants from a database of the Chemosensory Neuroanatomy Laboratory at Université du Québec à Trois-Rivières. We used a recruitment poster on social networks (Facebook) and word was spread around in the research team. The inclusion criteria were as follow: Women and men aged eighteen and more with no concussion and without any history of loss consciousness or any diagnosed of mental illnesses. They also needed to have normal olfactory capacities, as assured by the Sniffin'Sticks identification test (Hummel et al., 1997; Oleszkiewicz et al., 2018). Participants were asked not to wear any perfume and not to eat, drink and/or smoke 1h prior to the testing session. All of them gave written consent prior to testing.

Participants received 10 $ per hour as a financial compensation (average of 30$ per participants) and their parking fees were paid by the laboratory. This study was approved by the Ethics Committee in research with humans at Université du Québec à Trois-Rivières.

MATERIALS

Questionnaire

We used the validated French version of the State-Trait Anxiety Inventory questionnaire (STAI) to measure the levels of anxiety (Gauthier & Bouchard, 1993; Spielberger, 1970). This questionnaire consists of 40 items, divided into two 20 items scales, that estimates the trait and state anxiety, respectively. State anxiety can be defined as a measure of the immediate, or acute, level of anxiety, whereas trait anxiety reflects the long-term tendency of an individual to show an increased anxiety response (Gross & John, 2003). Participants were asked to estimate the intensity of their feelings on a 4-point Likert scale. Total score was calculated using the Likert points for the negative items, and the inverse for the positive items. A higher score indicated the higher levels of trait or state anxiety. The trait and state anxiety subscales both have a score range of 20 to 80. The questionnaire took about 10 minutes to complete.

Stimulation and recording of CSERP

To deliver the chemosensory stimulation in the same manner for each participant, we used a modular olfactometer OL023 (Burghart Messtechnik, Vedel, Germany). This device blows an 8L/min constant air flow into the participants' nostrils. It humidifies the air at about 60% and heats it to a temperature of 36.5 degrees Celsius to avoid irritation (Kobal & Hummel, 1988; Kobal, 1985).

We used two odorants with a generally positive valence, eucalyptol (eucalyptus odor; 25% concentration, Sigma-Aldrich, USA) for the mixed olfactory-trigeminal stimulus condition and phenyl ethanol (rose odor; 10% concentration, Sigma-Aldrich, USA) for the pure olfactory stimulus condition. About 5 ml of each odorant were placed into separate cylinders of the olfactometer. A third cylinder containing odorless water was used to send non-odorous stimulations. When a nostril received an odorant (eucalyptus or rose), the other nostril therefore received non-odorous air. Each stimulus lasted 200 ms with an inter-stimulus interval of 28–30 seconds to avoid habituation. The participants had to identify in which nostril the odorant had been presented.

To compensate for the cerebral activity produced by the sounds of the opening and closing valves of the olfactometer during the stimulations, the participants wore headphones in which rain sounds were played.

The electroencephalographic (EEG) data were recorded throughout the ERP experiment with a BrainVision Recorder, an actiCHamp amplifier and an ActiCap with 32 active electrodes from the Brain Vision series (BrainVision Products, Montreal, Canada). We placed the ActiCap according to the international 10–20 system (Klem et al., 1999). The Cz electrode was of interest to evaluate the electrophysiological modifications of the LPC component (Pause & Krauel, 2000). Two reference electrodes were placed on the mastoids and two additional electrodes were placed, one under the right eye and one over the left eye. As usual, we placed a ground electrode in the middle of the forehead of the participants, which allowed the system to calculate the impedances at each electrode. An estimate of 0.2-0.3 ml of the SuperVisc gel (BrainVision Products, Montreal, Canada) was inserted between the electrode and the participant's skin. Impedances were kept under 10 kΩ. Recordings were made with a 500 Hz frequency.

PROCEDURE

Participants were tested in 1 session that lasted approximately 2 hours. After obtaining consent, the olfactory capacities were measured using the Sniffin'Sticks identification task - participants with a score below 11 were not included in the study (Oleszkiewicz et al., 2019). Then participants were then seated on a comfortable chair, and we installed the 32-channels EEG cap. Before the experimental task began, participants completed the French version of the STAI. Following the completion of this questionnaire, instructions were given to the participant and the ERP session began.

During the ERP session, participants received 2 blocks of 40 olfactory stimulations. Per block, the participant received 20 stimulations per nostrils, in a pre-programmed order, which remained the same for each participant. Only one odorant was sent for each block (either rose or eucalyptus). The order of blocks was randomized. Each stimulus lasted 200 ms with an inter-stimulus interval of 28–30 seconds to avoid habituation.

During the whole procedure, participants had to fixate a computer screen in front of them. To prepare them for a stimulus, a white cross was presented in the middle of a computer screen for 10 seconds. Participants had to fixate the white cross and try not to blink because a stimulus was about to be delivered. The participants did not know when the stimulation was going to occur during the presentation of the cross. After each stimulus, the participants had to identify in which nostril they perceived the odorant by using a hand-held mouse and clicking on the left or right arrow. Each block took about 25 minutes to complete.

We asked the participants to remain focussed and warned them when alpha waves —an electrophysiological signature of drowsiness — were starting to appear on the live EEG recordings. We gave the participants the option of taking a small break between the blocks.

EEG PROCESSING

We processed EEG datas with the use of BrainVision Analyser 2 (BrainVision Products, Montreal, Canada). We segmented the EEG recordings into 1700 ms epochs, starting 200 ms before the stimulation (Rombaux et al., 2006). We then filtered the datas off-line using a high band-pass filter of 0.01 Hz and a low band-pass filter of 30 Hz. We added a 5 Hz filter to the HEOG. After baseline correction, we removed the epochs containing artifacts (eye movement and/or muscular activity exceeding 100 µV) with the use of the BrainVision Analyser program. Only the participants that had more than 10 artifact free recordings for the selected condition and a visible LPC on their average visualisation were kept for the statistical analysis (Rombaux et al., 2006).

We averaged the artifact-free recordings for each condition (independent of stimulated nostril) and subject, to get a single-subject wave. We then calculated the amplitudes of the LPC component with the "area information" function, while we used the "peak amplitude" function of BrainVision Analyser 2 (BrainVision Products, Montreal, Canada) to obtain the latency values. Based on the literature (K. Ohla & J. Lundström, 2013; Tateyama et al., 1998) and grand average, we used both functions for the period between 400 ms and 800 ms post-stimulation after (see Figure 1). We then analyzed the latency and amplitude of the LPC of each subject for both conditions with IBM SPSS Statistics 28.0. The Cz electrode was selected for analysis due to its excellent reliability in measuring late components of CSERPs (Thesen & Murphy, 2002) and the for the great visibility of the LPC on this particular electrode.

STATISTICAL ANALYSIS

We calculated the state and trait anxiety scores. We then computed Pearson correlations between the latency of the LPC component recorded at Cz, and the anxiety scores for both the mixed olfactory-trigeminal and the pure olfactory condition. We did similar Pearson correlations between the amplitude of the LPC component recorded at Cz and the two anxiety scores. To measure effect size of correlations, we used Cohen criteria's (Cohen, 2013).

RESULTS

We observed a significant negative correlation between the LPC latency at Cz and the state anxiety, but not the trait anxiety score for the mixed olfactory-trigeminal condition ($r(18) = -.513$; $p = .021$) (See figure 2a). In contrast, we did not find any significant linear correlation between LPC latency and both anxiety scores for the pure olfactory condition (See figure 2b). We did also not observe any significant linear correlation between LPC amplitudes and the anxiety scores in any condition. No significant differences were observed between sexes for the latency or LPC amplitude of the different conditions, with the exception of a significant difference in LPC amplitude for the pure olfactory condition ($t(18) = 0.89$; $p = 0.03$). Additionally, there were no associations between age and latency or LPC amplitude for the different conditions (see Table 2).

DISCUSSION

Our study suggests that higher state anxiety scores are associated with shorter LPC latencies for a mixed olfactory-trigeminal stimulus, but not for a pure odorant. According to Cohen's criteria (Cohen, 2013), the effect size of this relation is considered large. These results are in accordance with the hypothesis of a perceptual bias towards threatening stimuli for mixed olfactory-trigeminal stimuli, in line with the notion of the trigeminal system's protective role against environmental threats (Gerhold & Bautista, 2009). One of the major distinctions between the two chemosensory systems is that unlike olfaction, the trigeminal relays directly to the thalamus (Thaploo et al., 2022; Albrecht et al., 2010). The thalamus is a key region involved in the regulation of anxiety-related behaviors and may be involved in the anticipation of uncertain threats in anxious individuals (Geng et al., 2018; Mutic et al., 2017; Choi et al., 2012.). Specifically, noradrenergic cortical projections enhance activity in thalamic and sensory regions. This facilitates direct communication between the thalamus and amygdala, thereby potentializing physiological responses to threat stimuli (LeDoux, 1996; Öhman, 2005; McEwen & Gianaros, 2010; Rued et al., 2019). It is therefore possible that the early thalamic anticipation of threatening stimuli is partly responsible for the observation of a shorter LPC latency from those with a higher level of state anxiety as for the mixed olfactory-trigeminal stimulations, the trigeminal system which is connected with the thalamus is activated. Future studies should test this hypothesis by using functional Magnetic Resonance Imaging (fMRI).

No correlation was observed between LPC latency and trait anxiety. These results are in contradiction with our initial hypothesis and with studies that have found significant results supporting the presence of a perceptual bias in individuals with high trait anxiety. Yet, some studies suggest that trait anxiety is more related with interpersonal threat than with physical threat (Leal et al., 2017; Endler & Kocovski, 2001). If we follow this perspective with regards to our findings, it seems appropriate to assume that mixed olfactory-trigeminal stimulation corresponds more to physical than interpersonal threat.

We did also not observe any effect of anxiety on the amplitude of the LPC, in line with an earlier report showing that the LPC amplitude after an olfactory stimulation was not influenced by state and trait anxiety (Ohla & Lundström, 2013). To comprehend this, it may be worthy to look at the visual modality: here the literature is relatively heterogenous with regards to the effect of anxiety on the P300 amplitude, the analogue component of the LPC. For instance, while some researchers observed increased amplitudes in high non-pathological anxiety levels (Ioakeimidis et al., 2021), others observed opposite results (Rowe et al., 2021). The implication of working memory during the task (Rowe et al., 2021; Luck, 2014) could explain some of the discrepancies. Indeed, the amplitude of the P300 corresponds to the memory load and varies according to the frequency of stimulation and the difficulty of a task (Rowe et al., 2021). It is therefore possible that the heterogeneous results observed in the amplitude of the P300 are better explained by the choice of the protocol than by anxiety. This issue would be worth investigating in the context of the LPC.

An important limitation of this study is a relatively low statistical power. Indeed, the time required to complete the task combined with its repetitiveness led to the presence of alpha waves in some of the EEG recordings. Alpha waves are patterns of rhythmic electric impulses produced near the occipital region, usually when the participant is in a state of rest/when eyes are closed and have a frequency between 8 and 13 Hz (Moini & Piran, 2020). Since the effects of the olfactory stimulation were expected to be visible between 5 and 30 Hz, the presence of alpha waves ended up hiding the cerebral activity produced by the olfactory stimulation. Even if we asked the participants to remain awake, gave them warnings when alpha waves started to show on the live recordings and gave them breaks in between the stimulation blocks, many recordings had to be removed because the CSERP components were not visible and/or the participant did not have enough clean recordings to be kept in the statistical analysis. For the future, a task with a certain level of arousal could be added in the inter stimulus interval to keep participants vigilant Another limitation is that the valence of the odorants (rose and eucalyptus) was not rated by the participants. Although these odors are generally known to have a positive valence, we cannot guarantee that this is the case for our sample. Finally, this study does not allow for the establishment of a causal link. Future studies should replicate this study with an experimental protocol that includes a group of people with an anxiety disorder compared to a control group on chemosensory evoked potentials and a behavioral measure (e.g. reaction time).

CONCLUSION

We show that state anxiety is negatively correlated with the latency of the LPC occurring after mixed olfactory-trigeminal stimulation. This suggests that a higher level of state anxiety is associated to a faster perceptual response for mixed olfactory-trigeminal stimuli but not for pure olfactory stimuli. This result supports the hypothesis of a perceptual bias following a mixed olfactory-trigeminal stimulation. In future studies using CSERPs, anxiety level should be considered as it could potentially affect components characteristics.

CONFLICT OF INTEREST

None declared.

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DATA AVAILABILITY

The data underlying this article will be shared on reasonable request to the corresponding author.

REFERENCES

Albrecht, J., Kopietz, R., Frasnelli, J., Wiesmann, M., Hummel, T., et Lundström, J. N. (2010). The neuronal correlates of intranasal trigeminal function-an ALE meta-analysis of human functional brain imaging data. *Brain Res Rev, 62* (2), 183-196. doi : 10.1016/j.brainresrev.2009.11.001

Andersson, L., Sandberg, P., Olofsson, J. K., & Nordin, S. (2018). Effects of Task Demands on Olfactory, Auditory, and Visual Event-Related Potentials Suggest Similar Top-Down Modulation Across Senses. Chemical senses, 43(2), 129-134. https://doi.org/10.1093/chemse/bjx082

Arent, S. M. et Landers, D. M. (2003). Arousal, Anxiety, and Performance: A Reexamination of the Inverted-U Hypothesis. *Research Quarterly for Exercise and Sport, 74* (4), 436–444. doi: 10.1080/02701367.2003.10609113

Asutay, E., & Västfjäll, D. (2015). Negative emotion provides cues for orienting auditory spatial attention. Frontiers in Psychology, 6, 618.

Baraniuk, J. N., & Kim, D. (2007). Nasonasal reflexes, the nasal cycle, and sneeze. Current Allergy and Asthma Reports, 7(2), 105-111. https://doi.org/10.1007/s11882-007-0007-1

Bar-Haim, Y., Lamy, D., Pergamin, L., Bakermans-Kranenburg, M. J., & van, I. M. H. (2007). Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. Psychol Bull, 133(1), 1-24. https://doi.org/10.1037/0033-2909.133.1.1

Benarroch, E. E. (2010). Olfactory system. *Functional organization and involvement in neurodegenerative disease, 75*(12), 1104-1109. https://doi.org/10.1212/WNL.0b013e3181f3db84

Bensafi, M., Pierson, A., Rouby, C., Farget, V., Bertrand, B., Vigouroux, M., Jouvent, R., & Holley, A. (2002). Modulation of visual event-related potentials by emotional olfactory stimuli. *Neurophysiologie Clinique/Clinical Neurophysiology, 32*(6), 335-342. https://doi.org/https://doi.org/10.1016/S0987-7053(02)00337-4

Blackwood, D. H., et Muir, W. J. (1990). Cognitive brain potentials and their application. *Br J Psychiatry Suppl*(9), 96–101.

Brand, G. (2006). Olfactory/trigeminal interactions in nasal chemoreception. Neuroscience & Biobehavioral Reviews, 30(7), 908-917. https://doi.org/https://doi.org/10.1016/j.neubiorev.2006.01.002

Carlson, J. M. (2021). A systematic review of event-related potentials as outcome measures of attention bias modification. *Psychophysiology, 58* (6), e13801. doi: https://doi.org/10.1111/psyp.13801

Chen, D. et Dalton, P. (2005). The effect of emotion and personality on olfactory perception. *Chem Senses, 30* (4), 345-351. doi : 10.1093/chemse/bji029

Choi, J. M., Padmala, S. et Pessoa, L. (2012). Impact of state anxiety on the interaction between threat monitoring and cognition. *NeuroImage, 59*, 1912–1923. doi: 10.1016/j.neuroimage.2011.08.102

Clepce, M., Reich, K., Gossler, A., Kornhuber, J., & Thuerauf, N. (2012). Olfactory abnormalities in anxiety disorders. *Neuroscience Letters, 511*(1), 43-46.

Cohen, J. (2013). *Statistical power analysis for the behavioral sciences*. Routledge.

Cortese, B. M., Schumann, A. Y., Howell, A. N., McConnell, P. A., Yang, Q. X. et Uhde, T. W. (2018). Preliminary evidence for differential olfactory and trigeminal processing in combat veterans with and without PTSD. *Neuroimage Clin, 17*, 378-387. doi : 10.1016/j.nicl.2017.09.018

Croy, I., Schellong, J., Joraschky, P. et Hummel, T. (2010). PTSD, but not childhood maltreatment, modifies responses to unpleasant odors. *International Journal of Psychophysiology, 75*, 326-331. doi : 10.1016/j.ijpsycho.2010.01.003

Croy, I., Springborn, M., Lötsch, J., Johnston, A. N. B., & Hummel, T. (2011). Agreeable Smellers and Sensitive Neurotics – Correlations among Personality Traits and Sensory Thresholds. *PLOS ONE, 6*(4), e18701. https://doi.org/10.1371/journal.pone.0018701

Demattè, M. L., Österbauer, R., & Spence, C. (2007). Olfactory Cues Modulate Facial Attractiveness. *Chemical senses, 32*(6), 603-610. https://doi.org/10.1093/chemse/bjm030

Doty, R. L. (1997). Studies of Human Olfaction from the University of Pennsylvania Smell and Taste Center. *Chemical senses, 22*(5), 565-586. https://doi.org/10.1093/chemse/22.5.565

Doty, R. L., Brugger, W. E., Jurs, P. C., Orndorff, M. A., Snyder, P. J., & Lowry, L. D. (1978). Intranasal trigeminal stimulation from odorous volatiles: Psychometric responses from anosmic and normal humans. Physiology & Behavior, 20(2), 175-185. https://doi.org/https://doi.org/10.1016/0031-9384(78)90070-7

Eldar, S., Yankelevitch, R., Lamy, D. et Bar-Haim, Y. (2010). Enhanced neural reactivity and selective attention to threat in anxiety. *Biol Psychol, 85* (2), 252-257. doi : 10.1016/j.biopsycho.2010.07.010

Endler, N. S. et Kocovski, N. L. (2001). State and trait anxiety revisited. *J Anxiety Disord, 15* (3), 231-245. doi : 10.1016/s0887-6185 (01) 00060-3

Enoch, M.-A., White, K. V., Harris, C. R., Rohrbaugh, J. W., & Goldman, D. (2001). Alcohol Use Disorders and Anxiety Disorders: Relation to the P300 Event-Related Potential. Alcoholism: Clinical and Experimental Research, 25(9), 1293-1300. https://doi.org/https://doi.org/10.1111/j.1530-0277.2001.tb02350.x

Eysenck, M. W. et Calvo, M. G. (1992). Anxiety and performance: The processing efficiency theory. *Cognition and Emotion, 6*, 409–434. doi: 10.1080/02699939208409696

Filiou, R.-P., Lepore, F., Bryant, B., Lundström, J. N., & Frasnelli, J. (2014). Perception of Trigeminal Mixtures. Chemical senses, 40(1), 61-69. https://doi.org/10.1093/chemse/bju064

Frasnelli, J., Hummel, T., Berg, J., Huang, G., & Doty, R. (2011). Intranasal localizability of odorants: influence of stimulus volume. Chemical senses, 36(4), 405-410.

Frewen, P. A., Dozois, D. J., Joanisse, M. F. et Neufeld, R. W. (2008). Selective attention to threat versus reward: meta-analysis and neural-network modeling of the dot-probe task. *Clin Psychol Rev, 28* (2), 307-337. doi : 10.1016/j.cpr.2007.05.006

Friedland K., Harteneck C. (2017). Spices and Odorants as TRP Channel Activators. In: BuettnerA. editor. Springer handbook of odor. Cham: Springer International Publishing. p. 85–86.

Gauthier, J. et Bouchard, S. (1993). Adaptation canadienne-française de la forme révisée du State–Trait Anxiety Inventory de Spielberger = A French-Canadian adaptation of the revised version of Spielberger's State–Trait Anxiety Inventory. *Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement, 25* (4), 559-578. doi : 10.1037/h0078881

Geng, H., Wang, Y., Gu, R., Luo, Y. J., Xu, P., Huang, Y. et Li, X. (2018). Altered brain activation and connectivity during anticipation of uncertain threat in trait anxiety. *Hum Brain Mapp, 39* (10), 3898-3914. doi : 10.1002/hbm.24219

Gerhold, K. A. et Bautista, D. M. (2009). Molecular and Cellular Mechanisms of Trigeminal Chemosensation. *Annals of the New York Academy of Sciences, 1170* (1), 184–189. doi: https://doi.org/10.1111/j.1749-6632.2009.03895.x

Gross, J. J., & John, O. P. (2003). Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. J Pers Soc Psychol, 85(2), 348-362. https://doi.org/10.1037/0022-3514.85.2.348

Hanatani, T., Sumi, N., Taguchi, S., Fujimoto, O., Nan-No, H., & Takeda, M. (2005). Event- related potentials in panic disorder and generalized anxiety disorder.

Psychiatry and Clinical Neurosciences, 59(1), 83-88. https://doi.org/https://doi.org/10.1111/j.1440- 1819.2005.01336.x

Hedner, M., Larsson, M., Arnold, N., Zucco, G. M., & Hummel, T. (2010). Cognitive factors in odor detection, odor discrimination, and odor identification tasks. J Clin Exp Neuropsychol, 32(10), 1062-1067. https://doi.org/10.1080/13803391003683070

Hörberg, T., Larsson, M., Ekström, I., Sandöy, C., Lundén, P., & Olofsson, J. K. (2020). Olfactory Influences on Visual Categorization: Behavioral and ERP Evidence. *Cerebral Cortex, 30*(7), 4220-4237. https://doi.org/10.1093/cercor/bhaa050

Hummel, T., Sekinger, B., Wolf, S. R., Pauli, E. et Kobal, G. (1997). 'Sniffin' Sticks': Olfactory Performance Assessed by the Combined Testing of Odor Identification, Odor Discrimination and Olfactory Threshold. *Chemical Senses, 22* (1), 39-52. doi : 10.1093/chemse/22.1.39

Invitto, S., Piraino, G., Ciccarese, V., Carmillo, L., Caggiula, M., Trianni, G.,... Balconi, M. (2018). Potential Role of OERP as Early Marker of Mild Cognitive Impairment. *Front Aging Neurosci, 10*, 272. doi : 10.3389/fnagi.2018.00272

Ioakeimidis, V., Khachatoorian, N., Haenschel, C., Papathomas, T. A., Farkas, A., Kyriakopoulos, M. et Dima, D. (2021). State anxiety influences P300 and P600 event-related potentials over parietal regions in the hollow-mask illusion experiment. *Personality Neuroscience, 4*, e2. doi: 10.1017/pen.2020.16

Kadohisa, M. (2013). Effects of odor on emotion, with implications. *Front Syst Neurosci, 7*, 66. doi : 10.3389/fnsys.2013.00066

Klem, G. H., Lüders, H. O., Jasper, H. H. et Elger, C. (1999). The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. *Electroencephalogr Clin Neurophysiol Suppl, 52*, 3-6.

Kobal, G. 1985. (1985). Pain-related electrical potentials of the human nasal mucosa elicited by chemical stimulation. Pain, 22(2), 151-163. https://doi.org/https://doi.org/10.1016/0304-3959(85)90175-7

Kobal, G., & Hummel, C. (1988). 1988. Cerebral chemosensory evoked potentials elicited by chemical stimulation of the human olfactory and respiratory nasal mucosa. Electroencephalography and clinical neurophysiology, 71(4), 241–250. https://doi.org/10.1016/0168-5597(88)90023-8

Kontaris, I., East, B. S. et Wilson, D. A. (2020). Behavioral and Neurobiological Convergence of Odor, Mood and Emotion: A Review. *Front Behav Neurosci, 14*, 35. doi : 10.3389/fnbeh.2020.00035

Krusemark, E. A. et Li, W. (2012). Enhanced olfactory sensory perception of threat in anxiety: An event-related fMRI study. *Chemosensory Perception, 5*, 37–45. doi: 10.1007/s12078-011-9111-7

Krusemark, E. A., Novak, L. R., Gitelman, D. R., & Li, W. (2013). When the sense of smell meets emotion: anxiety-state-dependent olfactory processing and neural circuitry adaptation. *J Neurosci, 33*(39), 15324-15332. https://doi.org/10.1523/jneurosci.1835-13.2013

La Buissonnière-Ariza, V., Lepore, F., Kojok, K. M. et Frasnelli, J. (2013). Increased odor detection speed in highly anxious healthy adults. *Chemical senses, 38* (7), 577–584.

Leal, P. C., Goes, T. C., da Silva, L. C. F. et Teixeira-Silva, F. (2017). Trait vs. state anxiety in different threatening situations. *Trends Psychiatry Psychother, 39* (3), 147–157. doi: 10.1590/2237-6089-2016-0044

LeDoux, J. E. (1996). *The emotional brain*. New York: Simon & Schuster.

Luck, S. J. (2014). An introduction to the event-related potential technique (2nd ed.). The MIT Press.

Lundström, J. N., Seven, S., Olsson, M. J., Schaal, B., & Hummel, T. (2006). Olfactory Event-Related Potentials Reflect Individual Differences in Odor Valence Perception. Chemical senses, 31(8), 705-711. https://doi.org/10.1093/chemse/bjl012

McEwen, B. S. et Gianaros, P. J. (2010). Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. *Ann N Y Acad Sci, 1186*, 190-222. doi : 10.1111/j.1749-6632.2009.05331.x

Moini, J., & Piran, P. (2020). Chapter 6-cerebral cortex. Functional and Clinical Neuroanatomy, 177-240.

Moran, T. P. (2016). Anxiety and working memory capacity: A meta-analysis and narrative review. Psychol Bull, 142(8), 831-864. https://doi.org/10.1037/bul0000051

Mutic, S., Brünner, Y. F., Rodriguez-Raecke, R., Wiesmann, M. et Freiherr, J. (2017). Chemosensory danger detection in the human brain: Body odor communicating aggression modulates limbic system activation. *Neuropsychologia, 99*, 187-198. doi : 10.1016/j.neuropsychologia.2017.02.018

Ohla, K., & Lundström, J. (2013). Sex differences in chemosensation: Sensory or emotional? Frontiers in Human Neuroscience, 7, 607. https://doi.org/10.3389/fnhum.2013.00607

Ohman, A. (2005). The role of the amygdala in human fear: automatic detection of threat. *Psychoneuroendocrinology, 30* (10), 953-958. doi : 10.1016/j.psyneuen.2005.03.019

Oleszkiewicz, A., Schriever, V. A., Croy, I., Hähner, A., & Hummel, T. (2019). Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. European Archives of Oto-Rhino-Laryngology, 276(3), 719-728. https://doi.org/10.1007/s00405-018-5248-1

Oleszkiewicz, A., Schultheiss, T., Schriever, V. A., Linke, J., Cuevas, M., Hähner, A., & Hummel, T. (2018). Effects of "trigeminal training" on trigeminal sensitivity and self-rated nasal patency. Eur Arch Otorhinolaryngol, 275(7), 1783-1788. https://doi.org/10.1007/s00405-018-4993-5

Pacharra, M., Schäper, M., Kleinbeck, S., Blaszkewicz, M., Golka, K., & van Thriel, C. (2016). Neurobehavioral effects of exposure to propionic acid revisited—Does psychosocial stress interfere with distractive effects in volunteers? *NeuroToxicology, 55*, 102-111. https://doi.org/https://doi.org/10.1016/j.neuro.2016.05.019

Pause, B. M. et Krauel, K. (2000). Chemosensory event-related potentials (CSERP) as a key to the psychology of odors. *Int J Psychophysiol, 36* (2), 105-122. doi : 10.1016/s0167-8760 (99) 00105-1

Pause, B. M., Sojka, B., Krauel, K. et Ferstl, R. (1996). The nature of the late positive complex within the olfactory event-related potential (OERP). *Psychophysiology, 33* (4), 376-384. doi : 10.1111/j.1469-8986.1996.tb01062.x

Peschard, V., Maurage, P., & Philippot, P. (2014). Towards a cross-modal perspective of emotional perception in social anxiety: review and future directions. Front Hum Neurosci, 8, 322. https://doi.org/10.3389/fnhum.2014.00322

Pfaar, O., Raap, U., Holz, M., Hörmann, K., & Klimek, L. (2009). Pathophysiology of itching and sneezing in allergic rhinitis. Swiss Medical Weekly, 139(0304), 35-40.

Pollatos, O., Kopietz, R., Linn, J., Albrecht, J., Sakar, V., Anzinger, A., Schandry, R., & Wiesmann, M. (2007). Emotional stimulation alters olfactory sensitivity and odor judgment. *Chem Senses, 32*(6), 583-589. https://doi.org/10.1093/chemse/bjm027

Reeb-Sutherland, B. C., Vanderwert, R. E., Degnan, K. A., Marshall, P. J., Pérez-Edgar, K., Chronis-Tuscano, A., Pine, D. S., & Fox, N. A. (2009). Attention to novelty in behaviorally inhibited adolescents moderates risk for anxiety. Journal of Child Psychology and Psychiatry, 50(11), 1365-1372. https://doi.org/https://doi.org/10.1111/j.1469-7610.2009.02170.x

Robinson, O. J., Vytal, K., Cornwell, B. R. et Grillon, C. (2013). The impact of anxiety upon cognition: perspectives from human threat of shock studies. *Front Hum Neurosci, 7*, 203. doi : 10.3389/fnhum.2013.00203

Rombaux, P., Mouraux, A., Bertrand, B., Guerit, J. M., & Hummel, T. (2006). Assessment of olfactory and trigeminal function using chemosensory event-related potentials.

Neurophysiologie Clinique/Clinical Neurophysiology, 36(2), 53-62. https://doi.org/https://doi.org/10.1016/j.neucli.2006.03.005

Rowe, J., Ferguson, T. et Krigolson, O. (2021). Decision Making Under Chronic Stress and Anxiety: State and Trait Anxiety Impact Contextual Updating but not Feedback Learning. *The Arbutus Review, 12*, 84–103. doi: 10.18357/tar121202120178

Rued, H. A., Hilmert, C. J., Strahm, A. M. et Thomas, L. E. (2019). The influence of stress on attentional bias to threat: An angry face and a noisy crowd. *Psychonomic Bulletin & Review, 26*, 943-950. doi : 10.3758/s13423-018-1538-2

Shipley, M. T., & Ennis, M. (1996). Functional organization of olfactory system. *Journal of Neurobiology, 30*(1), 123-176. https://doi.org/https://doi.org/10.1002/(SICI)1097-4695(199605)30:1<123::AID-NEU11>3.0.CO;2-N

Singh, A. K., Touhara, K. et Okamoto, M. (2019). Electrophysiological correlates of top-down attentional modulation in olfaction. *Scientific Reports, 9* (1), 4953. doi: 10.1038/s41598-019-41319-6

Soudry, Y., Lemogne, C., Malinvaud, D., Consoli, S. M., & Bonfils, P. (2011). Olfactory system and emotion: Common substrates. *European Annals of Otorhinolaryngology, Head and Neck Diseases, 128*(1), 18-23. https://doi.org/https://doi.org/10.1016/j.anorl.2010.09.007

Spielberger, C. D. (1970). *The State-Trait Anxiety Inventory (test manual)*. Consulting Psychologists Press.

Sur, S. et Sinha, V. K. (2009). Event-related potential: An overview. *Ind Psychiatry J, 18* (1), 70–73. doi: 10.4103/0972-6748.57865

Takahashi, T., Itoh, H., Nishikawa, Y., Higuchi, Y., Nakamura, M., Sasabayashi, D., . . . Suzuki, M. (2015). Possible relation between olfaction and anxiety in healthy subjects. *Psychiatry Clin Neurosci, 69* (7), 431-438. doi : 10.1111/pcn.12277

Tateyama, T., Hummel, T., Roscher, S., Post, H. et Kobal, G. (1998). Relation of olfactory event-related potentials to changes in stimulus concentration. *Electroencephalogr Clin Neurophysiol, 108* (5), 449-455. doi : 10.1016/s0168-5597 (98) 00022-7

Thaploo, D., Joshi, A., Georgiopoulos, C., Warr, J. et Hummel, T. (2022). Tractography indicates lateralized differences between trigeminal and olfactory pathways. *Neuroimage, 261*, 119518. doi: 10.1016/j.neuroimage.2022.119518

Thesen, T., & Murphy, C. (2002). Reliability analysis of event-related brain potentials to olfactory stimuli. Psychophysiology, 39(6), 733-738. https://doi.org/https://doi.org/10.1111/1469-8986.3960733

Tremblay, C., & Frasnelli, J. (2018). Olfactory and Trigeminal Systems Interact in the Periphery. Chemical senses, 43(8), 611-616. https://doi.org/10.1093/chemse/bjy049

Viana, F. (2011). Chemosensory Properties of the Trigeminal System. *ACS Chemical Neuroscience, 2* (1), 38–50. doi: 10.1021/cn100102c.

Wysocki, C. J., Cowart, B. J., & Radil, T. (2003). Nasal trigeminal chemosensitivity across the adult life span. *Percept Psychophys, 65*(1), 115-122. https://doi.org/10.3758/bf03194788

FIGURES LEGENDS

Figure 1: Grand Average mixed olfactory-trigeminal (green) and pure olfactory (pink) conditions in CZ position. The identification of the time window for the LPC component was made between 400 and 800 ms.

Figure 2. Correlation between Late Positive Component (LPC) latency in Cz and state anxiety scores for both mixed olfactory-trigeminal (2a) and pure olfactory conditions (2b).