Research report

A role for the insula in color-induced nasal thermal sensations

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ABSTRACT

This article is the first step towards understanding the mechanisms underlying the intriguing, recently discovered lateralized color-induced nasal thermal sensations. In the presence of color cues and complete absence of thermal stimulus, larger sensitivity of the left nostril/right hemisphere (RH) for warming sensations and larger right nostril/left hemisphere (LH) for cooling sensations were replicated several times. It was suggested that engagement in a temperature judgment task and the development of specific expectancies due to the presence of color cues could alter and enhance processing in brain areas involved in thermosensory processing, such as the middle/posterior insula. The lateralized patterns could thus intimate hemispheric specialization for thermosensory processing. However, such lateralization may be due to either exclusive specialization of each hemisphere or specialization-through-reciprocal inhibition between the hemispheres. The two hypotheses predict different results following a unilateral insular stroke. Here, we present the results of a sample of healthy volunteers and patient MB, a young woman suffering from unilateral left-side damage of the posterior insula, in a task involving color-induced nasal thermal judgment. The expected lateralized pattern was found in the performance of the controls. In line with our previous suggestions that the LH is more involved in the processing of cooling sensations, patient MB exhibited changes only in the judgment of cooling sensations. Her results also clearly support the specialization-through-reciprocal inhibition account since she exhibited decreased cooling judgments contraterally but increased cooling judgments ipsilaterally. Accordingly, we conclude that (a) the lateralized patterns arise because of hemispheric specialization; (b) the LH is seemingly more involved in the processing of cooling sensations; (c) this specialization is underlain by reciprocal interhemispheric inhibition; and (d) even in the absence of thermal stimulus, the development of expectancies suffices to activate modality-specific brain areas involved in the current task in such a way that damage to these areas disturbs the corresponding specific processes.

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1. Introduction

Intriguing color-induced nasal thermal judgments in healthy volunteers have recently been reported and replicated several times [1,2]. In a standard trial, subjects are required to judge whether a sniffed bottle, presented out of sight and containing odorless water and free of any thermal agent, evokes cooling or warming sensations in the nasal cavity. The sniff is taken with one nostril while simultaneously viewing a different solution, colored red or green. Two distinct behaviors are detected: first, subjects do not use strategies such as frequently giving a response that matches the color viewed (e.g., warming with red, and cooling with green); second, they preferentially associate warming responses with red when the sniff is taken with the left nostril, while more frequently associating cooling responses with green when they sniff with the right nostril. These findings are robust enough to resist changes in methodology, even when subjects are allowed to give an additional “ambient” response. They depend on task difficulty and the presence of colors, and are specific to unilateral nostril stimulation. Evidence points to fairly high order cognitive processes being responsible for modulating nasal thermal judgments. Such processes are guided by color cues and likely to intervene through modulation of activity in areas specialized in temperature processing. One possible candidate is the insular thermosensory cortex [3].

Differences observed between nostrils suggest these effects may depend upon specialization of the cerebral hemispheres. Trigeminal projections arising in the nasal cavity and conveying thermal signals are mostly contralateral, i.e., signals from the right nos-
Fig. 1. (A) Graphic depiction of the hypothetical hemispheric functioning in normal subjects giving rise to lateralized color-induced nasal thermal judgments, and the
dysfunction predictions that can be made after unilateral brain damage. White bars represent expected responses to red solutions, and grey bars represent expected
responses to green solutions. “Cool” and “warm” denote specialized thermosensory neural circuits, with words in capitals denoting dominance. The upper part of the image
represents the exclusive specialization hypothesis and the lower part the specialization-through-reciprocal inhibition hypothesis. Dotted lines represent weakened activity.
LN, left nostril; RN, right nostril; LH, left hemisphere; RH, right hemisphere. Brain damage is shown with an X. Inhibitory activity is marked with a —. Note that, while the
exclusive and reciprocal inhibition hypotheses predict the same results under normal functioning, they predict different dysfunctions. See text for more details. (B) A front
view (upper image) of the Eyes/Nostrils Dissociation Device (ENDD) and a lateral view (lower image) showing how subjects and the experimenter were placed during the
Experiment.

... tril are conveyed to the left cerebral hemisphere (LH), and those from the left nostril to the right hemisphere (RH). Warming and cooling signals may thus be processed via selective pathways [4,5], giving rise to hemispheric differences [1]. Other than identifying a central role for the insular cortex in thermosensory processing, imaging studies have shed little light on the lateralization of these processes [3,6]. Craig et al. [3] reported activation of a mostly left-sided network in response to cooling stimuli involving the middle/posterior insula. There is also evidence that, along with somatotopic organization of pain [7], such thermosensory representations in the insula are somatotopographically organized [8]. The hemispheric account is supported by insular pathology. Birklein et al. [9] reported a selective loss of contralateral cold perception, without any loss of warm perception, following a lesion of the left insula. Conversely, Cattaneo et al. [10] reported a selective loss of contralateral warm perception, without any loss of cold perception, following a lesion of the right insula. Cooling and warming signals are seemingly processed separately. Such processing is probably lateralized, and involves the insular cortex. A key question [2] has to do with the nature of these lateralized patterns. Are they due to exclusive specialization of the cerebral hemispheres, or to specialization that arises as a result of inhibition between the hemispheres [11]. In the first case, each hemisphere would be more involved than the other in one particular type of processing. Both hemispheres would process thermosensory signals [12] at different degrees, with the LH specializing in cooling signals and the RH in warming signals. In the second case, in addition to their relative specialization, the specific thermosensory systems of the two hemispheres would be mutually inhibiting (e.g., the dominant LH processing of cooling signals would inhibit the non-dominant cooling system of the RH), so that each could efficiently process the signals it is specialized to process [11]. Neuropsychological evidence would considerably help disentangle these two accounts since each one predicts different results in patients suffering from a unilateral lesion, especially involving the posterior insula [3,12]. The first account would gather support if a simple reduction in the color–temperature associations were to be found for the nostril contralateral to the lesion, where, for example, the right nostril dominance of green-cooling responses would diminish following a unilateral lesion of the LH. Apart from this pattern, the second account predicts an additional one, namely the increment of these responses ipsilaterally due to the release from inhibition exerted by the damaged hemisphere on the intact one. As a point of fact, over-responsiveness to ipsilateral stimuli is one of the phenomena observed after release from inhibition, revealing a loss of interhemispheric balance. For instance, a diminishing of green-cooling responses in the right nostril after unilateral left lesion would be accompanied by a rise in such responses in the left nostril. If this rise exceeded the level of the ipsilateral red-warming responses, then a supplementary compensation effect could be suspected (i.e., once disinhibited, the hemisphere overreacts). The two hypotheses are graphically represented in Fig. 1 for a LH lesion.
Here, we present the results of a young female patient suffering from lesions involving a small portion of the left posterior insula. The patient developed neuropathic pain that was worsened by the use of cold colors (e.g., green or blue) for painting, suggesting some kind of color–temperature synaesthesia [12]. Since the lesion was in the left hemisphere and concerned the insula [3], it was expected that green-cooling associations would be affected when assessing color-induced nasal thermal judgments. On the basis of the exclusive specialization account, a decrement in the frequency of green-cooling responses was expected contralaterally (i.e., right nostril). Conversely, on the basis of the reciprocal inhibition account, it was expected that the contralateral decrement in the frequency of green-cooling responses would be accompanied by an ipsilateral (i.e., left nostril) increment of the same responses. Patient MB’s results are thus critical for disentangling these two accounts.

2. Methods

2.1. Case description

Patient MB, a right-handed woman (laterality coefficient 0.83) according to the Edinburgh laterality inventory [14], developed an acute idiopathic stroke in the left Sylvian artery territory in February 2007, at age 35. An MRI performed in February 2008 showed two left hemispheric lesions involving both a small portion of posterior insula (Talairach coordinates x = −41, y = −3, z = 0.6) and a deep part of SII cortex (x = −45, y = −12, z = 17). At the time, she was experiencing chronic severe neuropathic pain with permanent spontaneous burning sensations, combined with freezing cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb. An examination revealed she had a very severe allodynia with a with-freezing cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb. An examination revealed she had a very severe allodynia with a painful cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb. An examination revealed she had a very severe allodynia with a painful cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb. An examination revealed she had a very severe allodynia with a painful cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb. An examination revealed she had a very severe allodynia with a painful cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb. An examination revealed she had a very severe allodynia with a painful cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb. An examination revealed she had a very severe allodynia with a painful cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb. An examination revealed she had a very severe allodynia with a painful cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb. An examination revealed she had a very severe allodynia with a painful cold sensations, paresthesiae and electrical discharges, mainly on the right upper limb.

2.2. Control subjects

Thirty-three female volunteers (mean age: 36.6 ± 5.9 years) took part in this study. All had normal or corrected-to-normal vision and could correctly identify the colors of the stimuli. According to the Edinburgh laterality inventory [14], all were right handed (laterality coefficient: 0.87 ± 0.14). At the time of testing, they were not pregnant, non-smokers, free of sinus infection, allergy and hay fever, and not under medication. They all gave their written consent and participated with enthusiasm in this test in an effort to better understand her synaesthesiae (Fig. 2).

2.3. Stimuli

Three small 20 ml glass bottles (height: 5 cm; diameter: 3 cm) containing 10 ml of water were used as stimuli. One drop of odorless food coloring (Vahiné; H: 126; Saturation (S): 100%; Brightness (B): 88%) and one red solution (H: 0; S: 100%; B: 100%). The solution contained in the third bottle remained colorless. A yellow solution (H: 46; S: 100%; B: 100%) was used during training trials. The bottles were placed in a 30 cm × 10 cm × 7 cm box with eight empty glass bottles and were not visible to the participant.

2.4. Apparatus

The Eyes/Nostrils Dissociation Device (ENDD; Fig. 1A) was used, a white 40 cm high screen, specially designed for separating the visual and the olfactory input that the patient smells. The detailed description of this device can be found in [2]. It comprises two rectangular boards joined together; the lower one acts as a support while the upper one is used to present the colored solution and receives the subject’s nose bone. The nose-bone receptacle contains a small soft pad filled with cottonwool to maximize comfort, minimize thermal sensations on the skin caused by the wooden board, and, as far as possible, fit the shape of each subject’s nose bone, thereby separating their eyes from their nostrils. Another board is placed opposite the nose-bone receptacle to prevent the color of the objects behind the device interfering with the color of the solutions exhibited.

2.5. Procedure

The experiment was carried out in a quiet room under normal lighting conditions, and with an ambient temperature of 26 °C. The experimenter sat facing the subject, with a small table placed between them. On the table was a box containing the glass bottles and the ENDD. At the start of the test, the experimenter told the subject if the box contained a large number of bottles and then proceeded to touch them in order to produce a chime, so that the subject believed the box really did contain a large number of bottles and that a different one was presented in each trial. Subjects were not allowed to handle the bottles and were told that they all contained chemical agents, half of which would elicit cooling sensations and half warming sensations, but that these were so diluted that intuitive judgments could help. This method proved effective in previous studies on visual-somatosensory [16] and color–nasal temperature interactions [12] since it induces non-random response biases. Participants were then invited to get close to the ENDD and to position their head in such a way that they could no longer see their nose. The experimenter checked that their nose bone was correctly positioned in the receptacle and that their eyes were above the upper board of the stand with their nose below it (Fig. 1B). One of the bottles containing a colored solution was placed just in front of the viewing midline, at a distance of 33 cm from subjects’ eyes. The experimenter refrained from giving any information about the relation between the exhibited bottle and the sniffed bottle. Each trial started with the participant being asked to fixate the bottle and to maintain fixation throughout the whole trial. The experimenter checked the bottle was fixated and then asked the subject to close a designated nostril using the index finger of the hand of the same side (left hand for left nostril, right hand for right nostril). The bottle containing the colorless solution was then held up to the other nostril, and the subject was required to smell by taking one deep, slow sniff and to report whether the solution induced a cooling or warming sensation in the nasal cavity. No other response was accepted. Subjects were completely unaware of the fact that they were always sniffing the same bottle containing a colorless, odorless and trigeminal-free solution presented at ambient temperature. Two factors were manipulated, each having two levels: (a) the tested nostril (left or right) and (b) the color of the exhibited solution (red or green). Six trials were presented per condition, and each of the four conditions was counterbalanced across trials and across subjects in a complete latin square order. The number of trials was based on pilot experiments conducted on healthy volunteers of different ages (20s, mid-30s and mid-50s) having shown that the expected nostril by color patterns were robust up until 6 trials per condition, diminished with 8 trials, and disappeared with 12 trials or more (up to 24 presented), a phenomenon mainly explained by decreasing motivation over time as retrospectively suggested by subjects. The test was preceded by a few training trials during which the exhibited bottle contained a yellow solution. The Experiment lasted 10 min. Responses were recorded by the experimenter.

3. Results

3.1. Control subjects

An analysis of variance (ANOVA) was carried out on the proportions of expected responses, that is, the number of red-warming and green-cooling associations. The tested nostril (left vs. right) and color of the exhibited solution (red vs. green) were the within-subject factors. The main effect of nostril failed to reach significance (left: 0.48; right: 0.53; F(1, 32) = 3.3; P = 0.07), as did the main effect of color (red: 0.49; green: 0.51; F(1, 32) = 0.21; P > 0.64). The nostril × color interaction was significant (F(1, 32) = 8.95; P < 0.0054; Fig. 3). Planned comparisons (t-tests) revealed that, when the left nostril was stimulated, the proportion of red-warming (0.53) responses was greater than the proportion of green-cooling responses (0.42; P < 0.0038), and the exact opposite pattern was found when the right nostril was stimulated (red: 0.45; green: 0.60; P < 0.007). For avoiding any probable misinterpretations, the results were also analyzed by submitting ‘warming’ responses (instead of expected responses) to an ANOVA with the tested nostril and the exhibited color as within-subjects factors. The results were similar to those observed with expected responses in that the nostril × color interaction was significant (F(1, 32) = 4.61; P < 0.039). The results of the controls are thus very similar to those reported earlier [1,2], even though this group is older than those tested in our previous studies. Red-warming responses were more frequent for the left nostril, and green-cooling responses more fre-
quent for the right nostril. This is consistent with hemispheric lateralization patterns.

3.2. Patient MB

The case–controls comparison was carried out using the $Q'$ test [17,18] with the tested nostril (left vs. right) and color of the exhibited solution (red vs. green) as factors. This entails converting the mean RT of each condition into z values based on the mean and SD of the controls, and then comparing the corresponding point estimates (i.e., proportions of subjects obtaining less extreme scores than the case). The nostril × color interaction was highly significant ($Q'(1) = 39.7; P < 0.00001$). The presence of such an interaction in a case–control analysis suggests the performance of patient MB did not match the expected crossed pattern found in the controls’ performance (Fig. 3). A closer inspection showed that, when viewing a red solution, patient MB’s warming responses were no different to those of the controls, whether the solution was presented in the right (0.5; $Q' = 1.06; P > 0.14$) or left (0.5; $Q' = -0.67; P > 0.25$) nostril. Significant differences were found, however, with green solutions (i.e., cooling responses). However, MB’s proportion of green-cooling responses was significantly lower than that of controls when the right (contralateral) nostril was stimulated (0.5; $Q' = -2.39; P < 0.009$) and higher when the left (ipsilateral) nostril was stimulated (0.83; $Q' = 5.57; P < 0.00001$). These results clearly show that the proportion of green-cooling responses diminished contralaterally and increased ipsilaterally.

4. Discussion

The nostril-by-color interaction was evidenced in the performance of the controls, with an impressive crossed pattern suggesting a left nostril dominance (RH) for warming judgments and a right nostril (LH) dominance for cooling judgments. This result is fairly consistent with those presented in our previous studies [1,2]. From a general, theoretical point of view, it was suggested that the combined activity of learned-based expectations and neurobiological wiring might determine these effects. Acquired color–temperature associations would elicit task-dependent perceptions in another modality (i.e., if the judgment to be made concerns temperature the elicited percept would be thermosensory in nature, whilst it would be olfactory if the judgment were an olfactory one). Thus, engagement in a task could alter and enhance processing in modality-specific brain areas mostly through expectations of the observer. Research in the fields of vision [19], audition [20], olfaction [21], somesthesis [22], and gustation [23,24] support this account. The fact that lateralized patterns are observed only when color cues are available [1,23] suggests thermosensory perceptions elicited by temperature-related colors in a task of temperature judgment arise from specialized lateralized neural pathways. Innocuous thermoreceptors terminate in the superficial spinal and trigeminal dorsal horn where a unique population of neurons is thermoreceptive-specific. These neurons project to the posterior part of the ventral medial nucleus of the thalamus (VMpo) and reach a cytoarchitectonically distinct field in the posterior insular cortex [3]. Lesions of the dorsal posterior insula reduce or eliminate contralateral thermal sensation in humans [9,10,25], and its electrical stimulation can result in thermal sensations [26]. Since the discriminative thermosensory cortex seemingly lies in the middle/posterior insula [3,8], it is plausible that this region is involved in the color-induced nasal thermal sensations and that at some degree it may exhibit a hemispheric specialization [9,10].

According to this hypothesis, lesions of the posterior insula would result in diminished contralateral thermal sensitivity and, a minima, diminished contralateral color–temperature associations depending on the damaged hemisphere (red-warming for lesions of...
the RH and green-cooling for lesions of the LH. In agreement with this, the QST of patient MB revealed the expected contralateral thermosensory hypoesthesia [13], and the results of our study showed a reliable decrement in nasal thermal judgments only for green-cooling responses compared to the sample of control subjects. The contralateral red-warming responses underwent no change, and the overall contralateral pattern of performance (i.e., right nostril) is consistent with psychophysical and neuropsychological evidence that the left hemisphere [1,2], in particular the insula [9], specializes more in processing cooling sensations than warming sensations. If this result were all that was evidenced in this study, no further discussion would be needed about the potential hemispheric specialization of thermosensory processing. However, evidence of an astonishing ipsilateral (i.e., right nostril) pattern makes further discussion essential. While compared to controls no significant change was observed for red-warming responses, a spectacular increment in the frequency of green-cooling responses was found. The fact that this pattern was an increment (as opposed to the contralateral decrement) and concerned only the green-cooling responses (just as with the contralateral pattern) is essential for understanding hemispheric mechanisms for processing thermal sensations. First, it implies that the left hemispheric lesion of patient MB affected only cooling judgments and, by extension, that the LH is mostly involved in processing cooling sensations. Second, the exclusive hemispheric specialization account is strongly challenged; otherwise only the contralateral decrement would be found. The overall pattern of green-cooling responses suggests the lateralized patterns probably emerge through reciprocal inter-hemispheric inhibition. According to Kinsbourne [11], behavior control is achieved through equilibration between the selection of specialized modality-specific brain areas involved in the current task and the reciprocal inhibition enabling equivocal choice between activating more the left of the right hemisphere. Thus, coactivation of both hemispheres moderates their competition. In the context of the present study, this point of view suggests that both hemispheres would be coactivated during nasal thermal judgments, but that reciprocal inhibition would determine which is most concerned at a given moment in time, depending on its specialization. The notion of reciprocal inhibition between systems specialized in processing the same signals (e.g., the system of the LH that processes preferentially cooling signals would inhibit its counterpart in the RH, and vice versa for warming signals) may explain the results obtained with patient MB. If we accept that the LH was more involved in processing cooling signals and that it exerted inhibitory control on the equivalent system in the RH, then damage to the LH should produce disinhibition of the RH. This would result in the pattern observed with patient MB’s results, in other words both decreased green-cooling responses contralaterally and a concomitant increment of these same responses ipsilaterally. The results of patient MB also suggest that the RH is over-responsive to green stimuli once released from inhibition. This is an expected behavior if it is admitted that coactivation of the two hemispheres confers balance during nasal judgments. A similar over-responsiveness of the intact hemisphere is admitted in spatial neglect. We can therefore conclude that reciprocal inhibition is better able to account for the results than exclusive specialization.

It is noteworthy that nostril dominance as a function of the color–temperature association arises when always sniffing the same colorless, odorless and trigeminal-free solution out of sight while simultaneously viewing another, colored solution. The effect is determined by the presence of color and unilateral stimulation of a thermosensitive sensory system [2]. In our model [1,2], involvement of modality-specific brain areas occurs as a function of expectations generated owing to the presence of color cues and engagement in a given task. In particular, the presence of color cues and engagement in a nasal temperature judgment task would result in involvement of the thermosensory insular cortex even in the absence of thermal stimulus. Patient MB’s performance reflects what happens when, as a result of damage, expectations and engagement in a task fail to activate the thermosensory insular cortex. The suggestion is therefore that the insular cortex would appear to be involved in the thermosensory percept elicited by
color cues. Overall, that insular damage should alter the pattern of results in the expected directions (contralateral decrement and ipsilateral increment in the frequency of green-cooling responses) adds further support to our model [1,2]. Seemingly, expecting a stimulus is sufficient for the thermosensory cortex to be involved and for lateralized nasal thermal judgments to arise, even though this stimulus is not delivered [16].

Aside from their associations with temperatures, colors are sometimes associated with emotions too. Patient MB’s neuropathic pain was worsened by using cold colors for painting, considering them negative [13] and this observation, completed with the results of the present study, suggest that the insular-SII cortices could be considered as a crossroad between sensory, emotional and motivational functions. In theory, synaesthesia can occur between or within any of the senses, the most common activation being color and the most common stimuli to cause it are days of the week or letters of the alphabet. Patient MB experienced displeasure and oppression when painting with cold colors, yet still being able to use them. This unusual combination between color temperature, somatosensory perception (including pain) and emotion that could be qualified as acquired synaesthesia, was involuntary in this patient, suggesting a new perceptual experience after brain damage. Interestingly, this experience was neither modulated by motivations (it was observed for spontaneous as well as for ordered creations), nor by painting techniques or levels of abstraction. Further investigation of the links between colors, somesthesia and emotion would thus be of central interest in our effort to understand potential insular lateralization.

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References