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Multisensory integration, body representation and hyperactivity of the immune system

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ABSTRACT

Multisensory stimuli are integrated over a delimited window of temporal asynchronies. This window is highly variable across individuals, but the origins of this variability are still not clear. We hypothesized that immune system functioning could partially account for this variability. In two experiments, we investigated the relationship between key aspects of multisensory integration in allergic participants and healthy controls. First, we tested the temporal constraint of multisensory integration, as measured by the temporal binding window. Second, we tested multisensory body representation, as indexed by the Rubber Hand Illusion (RHI). Results showed that allergic participants have a narrower temporal binding window and are less susceptible to the RHI than healthy controls.

Overall, we provide evidence linking multisensory integration processes and the activity of the immune system. The present findings are discussed within the context of the effect of immune molecules on the brain mechanisms enabling multisensory integration and multisensory body representation.

1. Introduction

The ability of the brain to integrate information coming from different modalities (namely Multisensory Integration) is fundamental for a number of cognitive processes ranging from detection and response to environmental stimuli (Diederich & Colonius, 2004; Frassinetti, Bolognini, & Làdavas, 2002; Lovelace, Stein, & Wallace, 2003; Meredith & Stein, 1983; Stein & Stanford, 2008) to the generation of a coherent multisensory representation of the body (Blanke, 2012; Ehrsson, 2012).

Several factors determine whether multisensory stimuli are integrated. The temporal relationship between the stimuli is one of the most important of such factors (e.g. Alex et al., 1987; Meredith & Stein, 1986). In fact, multisensory stimuli are more likely to be integrated when the stimuli fall in a limited range of asynchronies (in the order of hundreds of milliseconds), as compared to stimuli unrelated in time (e.g. Alex et al., 1987; Conrey & Pisoni, 2004; Radeau & Bertelson, 1987; Schall, Quigley, Onat, 2009). A large number of studies has been carried out to characterize several features of this time window of multisensory integration, usually referred to as the temporal binding window (TBW) (e.g. Noel, Wallace, Orchard-Mills, Alais, & Van der Burg, 2015; Stevenson & Wallace, 2013).

An aspect that stands out from these studies is that there are large individual differences in the temporal constraints of multisensory integration (Miller & D'Esposito, 2005; Stevenson, Zemtsov, & Wallace, 2012). However, the causes of this variability are

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currently unknown. In light of recent evidence, we propose that the immune system plays a role in modulating multisensory integration processes and, in particular, the individual temporal resolution in the perception of multisensory asynchronies.

The immune system is composed of a large number of cells (like phagocytic cells, cells that release inflammatory mediators and natural killer cells) and molecules (e.g. complement proteins, acute-phase proteins and cytokines, such as Interleukins) (Delves, Roitt, & Ivan, 2000). The main feature of these cells and molecules is that they are specialized in defending the organism (the host) against infection.

However, in recent years, research started unfolding a new, surprising role of the immune system; that is, the important role that this system plays in modulating the activity of the brain (Boulanger, 2009; Boulanger & Shatz, 2004; Kipnis, Gadani, & Derecki, 2012; Louveau, Harris, & Kipnis, 2015).

Everyone has experienced at least once a clear example of how immune molecules can influence the activity of the brain; that is, during states of infection. When people are sick, they go through a complex change in their behavior (referred to as sickness behavior, Dantzer, Kelley, & Adaptatifs, 2008) that includes social withdrawal, loss of appetite, and lethargy (Kent, Bluthé, Kelley, & Dantzer, 1992). People usually regard these reactions as the consequence of the debilitation process caused by infection. They are actually the result of an adaptive regulation of neural homeostasis exerted by immune molecules. The purpose of this regulation is to reorganize the behavior and resources of the host in order to minimize the exposure to new pathogens while fighting the infection (Bluthé, Michaud, Poli, & Dantzer, 2000; Filiano, Gadani, & Kipnis, 2015).

As stated above, the action of immune molecules in the CNS extends well beyond defense against infection (for a review, see McAfoose & Baune, 2009). For instance, in a series of animal model studies, Kipnis, et al. (2012) showed that T-cells stimulate meningeal immune cells to assume a pro-cognitive action, which results in an improvement of cognitive functions (e.g. improved learning behavior, Ziv et al., 2006). Some evidence of a relationship between the immune system and multisensory integration comes from Barnsley et al. (2011). Given the tight relationship between the cortical representation of body ownership and the physiological regulation of the body (e.g. Moseley et al., 2008), Barnsley and colleagues reasoned that inducing a sense of disownership over one's own arm would induce an elevated reactivity of the immune system. To test this hypothesis, they used a multisensory illusion, namely the Rubber Hand Illusion (RHI, Botvinick & Cohen, 1998), in order to induce in participants a sense of ownership over an artificial hand. In the RHI, delivering conflicting sensory (visual-tactile) stimuli induces, in most participants, a recalibration of one's body representation and a sense of ownership over an artificial limb (Botvinick & Cohen, 1998; Tsakiris & Haggard, 2005). Results validated the initial hypothesis by showing higher histamine reactivity in a participant's disowned arm as compared to the control arm and either arm in the control condition (Barnsley et al., 2011). In other words, inducing a recalibration of the multisensory body representation with the RHI affected the responsiveness of the immune system. While providing evidence of a relation between the multisensory representation and the immune system, this study leaves open the question of whether the inverse influence is possible; that is, whether the activity of immune molecules can affect multisensory integration processes. Recent work from our group provided some evidence of a relationship between the two. In particular, in a previous study we found a wider temporal window of multisensory integration in obese people, in whom metabolic alterations and a state of low-level inflammation are often clinically observed (Scarpina et al., 2016). Also, we found that multisensory body representation (as assessed by the RHI) is altered in participants suffering from coeliac disease, an autoimmune disorder characterized by high systemic levels of pro-inflammatory cytokines (Finotti & Costantini, 2016). Drawing upon this evidence, we asked whether immune dysregulations could affect basic functions of multisensory integration. In particular, we focused on a key aspect that affects Multisensory Integration: the individual's ability to discriminate temporal asynchronies of multisensory stimuli (e.g. Costantini et al., 2016). The present series of experiments was developed to explore this issue.

In the first study, we investigated whether the temporal sensitivity in the discrimination of multisensory stimuli is altered in drug-free subjects suffering from allergy, a medical condition characterized by a hyperactivity of the immune system (Ono, 2000; Toda & Ono, 2002). We tackled this question by using a simultaneity judgment task (SJ; Vroomen, Jean, Keetels, 2010). This paradigm allows us to calculate, across several stimulus onset asynchronies, the range of time in which stimuli are likely to be judged as concurrent (i.e. the temporal binding window, TBW; Murray & Wallace, 2011). Processing the temporal relationship between multisensory, interoceptive and exteroceptive stimuli is also crucial for the generation of a coherent multisensory representation of the body (e.g. Costantini et al., 2016). Therefore, in a second study, we aimed to investigate whether allergy affects the construction of a multisensory body representation. In accordance with past literature, we investigated the body representation using the rubber hand illusion (Botvinick & Cohen, 1998).

2. Experiment 1

2.1. Materials and methods

2.1.1. Participants

Fifty-one participants (mean age = 21.2; SD = 2.45; 45 female) took part in the study. Twenty-five participants had a history of allergy (mean age = 21.4; SD = 3.1; 20 female) Twenty-six participants were healthy individuals (mean age = 21.0; SD = 0.9; 25 female). In allergic participants, the disease was proven by skin prick test performed at the time of diagnosis. Most of the subjects suffered from more than one type of allergy, with an allergy to dust mites being the most common (14 subjects), followed by animal dander (8 subjects), pollen and grasses (8 subjects), food (4 subjects) and nickel (2 subjects). Participants were not taking drugs at the time of testing. All participants had normal or corrected to normal vision. Participants provided their written informed consent to participate in the study and were informed that they were free to abandon the experiment at any time. The study was approved by the