Acquisition and generalization of cough trigger beliefs in allergic rhinitis.

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Abstract

In allergic conditions, trigger identification is often inaccurate, and may be influenced by pre-existing beliefs. In this study, we investigated the acquisition and generalization of symptom trigger beliefs in individuals with allergic rhinitis (n=24) and control participants (n=24). In a lab-based trigger acquisition task, unique exemplars of two trigger categories were either paired with saline inhalation (CS- category) or citric acid inhalation (CS+ category). The next day, we tested recognition and symptom expectancy for CS category exemplars and exemplars of novel trigger categories. Participants acquired differential symptom expectancies for CS+ compared to CS- exemplars, with faster acquisition in participants with rhinitis. Differential symptom expectancies persisted the next day, and generalized to novel trigger categories, with stronger generalization in rhinitis vs. control participants. These patterns of acquisition and generalization suggest that overgeneralization of trigger beliefs may complicate trigger identification in participants with allergic conditions.

Keywords: generalization, trigger identification, allergy, cough, rhinitis, associative learning.

Introduction

Allergic rhinitis – commonly known as hay fever – is a chronic condition, characterized by inflammation of the nasal airway and symptoms such as nasal congestion, increased mucous production, itch, sneeze, and cough (Greiner, Hellings, Rotiroti, & Scadding, 2012). Individuals with allergic rhinitis can display sensitivity to a wide variety of environmental triggers, including aeroallergens and irritants (Bousquet et al., 2008; Greiner, et al., 2012). Allergic rhinitis shares characteristics with asthma; an inflammatory condition of the lower airways in which symptoms (shortness of breath and cough) are triggered by similar aeroallergens and irritants (Bousquet et al., 2008). In individuals with allergic rhinitis, the estimated prevalence of comorbid asthma is ranges from 20% in population studies to 48% in studies conducted in specialist care settings (Antonicelli et al., 2007; Bauchau & Durham, 2005). Differences in exposure to allergens and irritants, and individual variability in allergen sensitivity can lead to inter-individual and within-individual differences in symptom expression (Schatz, 2007).

Treatment guidelines for allergic rhinitis propose optimal treatment strategies consist of a combination of pharmacological treatment (antihistamines and/or nasal corticosteroids), trigger identification, and behavioral management consisting of trigger avoidance (e.g. staying away from pets, not running outside during allergy season, ...) or eradication of triggers through different interventions (e.g. removal of pets, mattress covers, ...) (Bousquet, et al., 2008; Braido, Arcadipane, Marugo, Hayashi, & Pawankar, 2014). However, interventions aimed at trigger avoidance and trigger eradication have been poorly tested, and have shown equivocal results (Custovic and van Wijk, 2005; Gøtzsche and Johansen, 2008).

One reason for the reduced efficacy of trigger avoidance measures may be that individuals with allergic conditions can be unaware, unsure or inaccurate about their personally relevant triggers. Studies that have investigated correspondence between patient

trigger beliefs and allergic response to specific allergens (using skin prick tests) in individuals with asthma and allergic rhinitis have shown that inaccurate identifications are common (Li, Andrist, Bamlet, & Wolter, 2000; Smith, Hogger, Lallemand, Crook, & Frew, 2009), and that patient ratings of symptom severity show only moderate to low correspondence with severity of allergic response to specific allergens (Graif, Goldberg, Tamir, Vigiser, & Melamed, 2006; Ritz, Steptoe, Bobb, Harris, & Edwards, 2006).

The difficulty of identifying symptom triggers is not unique to individuals with asthma or allergic rhinitis, but is a common feature of chronic conditions that are characterized by variable symptoms, such as food allergy/hypersensitivity, chronic migraine, and rheumatoid arthritis (Kelman, 2007; Pereira et al., 2005; Redelmeier and Tversky, 1996). Furthermore, identification and mis-identification of symptom causes is a key component of Leventhal's common sense framework (Leventhal, Breland, Mora, & Leventhal, 2010; Leventhal, Phillips, & Burns, 2016). According to this model, interpretation of illness-related information is driven by illness representations that include beliefs about causes, resulting in variation in symptom perception and illness-related actions (see also Petersen, van den Berg, Janssens, & Van den Bergh, 2011). In asthma and allergic rhinitis, a large body of research confirms the impact of illness representations on clinical outcomes (Braido et al., 2014; Kaptein, Klok, Moss-Morris, & Brand, 2010). However, research on the development of illness representations has been lacking, although general consensus is that these beliefs are shaped by experience and other forms of learning (Leventhal, et al., 2010). Focusing on trigger beliefs, Janssens and colleagues have conceptualized the identification of personally relevant symptom triggers as a contingency learning task involving motivationally relevant outcomes (danger and safety) (Janssens, Martens, Storms, & Van den Bergh, 2015; Janssens and Ritz, 2013). When confronted with a variety of potential triggers, individuals are faced with the challenge to gain information about which of these potential triggers are dangerous

(eliciting symptoms), and which of them are safe (not eliciting symptoms). Conceptualized in this way, learning about symptom triggers is similar to learning about predictors of aversive outcomes in the development of fear (Janssens, et al., 2015). Interestingly, the development of maladaptive fear and anxiety (e.g. anxiety disorders such as phobias, panic disorder, and generalized anxiety disorder) has been characterized by problems in this learning process, such as a difficulty in safety learning, or an (over)generalization of fear to stimuli that are similar to the original unpleasant situation (Haddad, Pritchett, Lissek, & Lau, 2012; Lissek et al., 2010; Lissek et al., 2009). Although generalization can be a helpful strategy to expand knowledge based on a limited number of learning experiences, overgeneralization can be problematic. In the case of allergic conditions such as asthma or allergic rhinitis, overgeneralization would result in an abundance of false positive triggers and associated trigger avoidance strategies, which in turn are associated with activity limitations and reduced quality of life (Janssens and Harver, 2015; Janssens and Ritz, 2013; Ritz, et al., 2006). Furthermore, allergic symptoms are sensitive to effects of expectancy and classical conditioning, in which symptoms can be evoked in response to cues or expectations that were paired with symptoms (De Peuter et al., 2005; Jaén and Dalton, 2014; Vits et al., 2011; von Leupoldt and Dahme, 2012). As effects of conditioned symptom cues can generalize to other similar cues (Devriese et al., 2000), generalized trigger beliefs may have a direct impact on symptom experiences, resulting in symptoms when individuals are confronted with these generalized symptom triggers.

In a proof of concept study in healthy participants, Janssens and colleagues demonstrated that methods derived from fear generalization research can be used to investigate generalization of symptom trigger beliefs (Janssens, et al., 2015). Using a trial-unique differential conditioning procedure (Dunsmoor, Martin, & LaBar, 2012), sham-exposure to allergens from one trigger category (CS+ category, e.g. mammals) had a 50% chance of

being followed by respiratory symptoms induced by brief inhalations of CO₂-enriched air, whereas sham exposure to allergens from the other category (CS- category, e.g. flowers) were never followed by symptoms. Crucially, individual triggers were not repeated during acquisition, making it necessary for participants to incorporate knowledge about trigger categories to inform trigger-symptom expectations. Symptom expectancy ratings during acquisition showed differential acquisition of trigger beliefs based on previously acquired conceptual knowledge (category membership). Furthermore, generalization tests using triggers from CS+, CS- as well as generalization categories (e.g. birds, molds) showed that acquired trigger beliefs generalized to novel exemplars of the CS+ category, as well as to exemplars of the generalization category that was most similar to the CS+ category, highlighting the interaction of higher order cognition and associative learning in the generalization of symptom triggers (cf. (Dunsmoor and Murphy, 2015; Dymond, Dunsmoor, Vervliet, Roche, & Hermans, 2015) for an overview of similar findings in the domain of fear learning).

In this study, our primary aim was to use the previously developed lab task to investigate the acquisition and generalization of cough trigger beliefs in a clinical population of individuals with respiratory allergies. We therefore recruited a group of participants with allergic rhinitis, as most clinical studies on inaccurate self-reports of triggers were carried out in individuals with this condition (Graif et al. 2006, Li et al. 2000, Smith et al., 2009). We further adapted the lab task to increase the ecological validity and relevance of the task for individuals with allergic rhinitis, as well as improving the duration of the experiment, by replacing inhalation of CO₂-enriched air with citric acid to induce cough/urge-to cough responses in the trigger acquisition task.

Methods

Participants

Participants were 48 college-aged individuals (41 female, ages 18-25). Half of the participants had a self-reported diagnosis of allergic rhinitis, the other participants served as the control group. Participants were recruited using posters in university buildings and posts on university social media outlets. The advertisements framed the experimental task as a validation study for a novel allergy test. Exclusion criteria were pregnancy, a history of chronic disease other than allergic rhinitis, poor lung function ($FEV1 < 80\%$ predicted), current cigarette smoking (1 or more cigarettes in the past week), and symptoms of common cold in the past week. The experiment was approved by the Medical Ethical Committee of University Hospitals Leuven (ID: S56347). Four participants (2 control participants) did not reach the C3 criterion during threshold test, and therefore did not participate in trigger acquisition and generalization. Age and gender of the participants completing the experiment are reported in Table 1. Due to problems with data acquisition, data on self-reported cough triggers was missing for 5 (3 control) participants. Participants with allergic rhinitis reported a higher incidence of allergic triggers, but not other cough triggers (full results cf. Table 1).

Trigger stimulus set

For the trigger acquisition and generalization we used pictures from a stimulus set of potential allergens, which consists of four allergen categories: mammals, birds, flowers, and molds, each consisting of 20 unique pictures (Janssens, et al., 2015). A key feature of this stimulus set is that pairs of allergy categories differ in conceptual similarity (e.g. mammals are more similar to birds than they are to flowers or molds, cf. Table 2), which allows us to investigate effects of category membership on the acquisition and (over)generalization of trigger-symptom expectancies.

Citric acid-induced cough

Cough provocation was performed using 2s single breath inhalations of citric acid, diluted in an isotonic saline solution. Citric acid was delivered using a compressed air-driven dosimeter (Jaeger APS, Hoechberg, Germany). During cough provocation, cough sounds were recorded with a tie clip microphone (ECM-2005, Monacor International, Bremen, Germany), connected to a laptop equipped with Adobe Audition (Adobe Systems, San Jose, CA), sampling the sound at 44.1 kHz. Cough frequency was assessed by two raters, who were blinded to participant information and the experimental condition in which the sound was recorded. For each cough recording, every cough-like expulsive event occurring during a 30 s epoch after dosimeter activation was scored as a single cough, regardless of inspiratory efforts in-between. Inter-rater reliability was estimated based on a subset of 44 cough recordings, and raters achieved a high reliability (ICC= .98 [95% CI .96-.99]).

Self-report measures

Participants rated symptom expectancy in response to the trigger pictures on a horizontal visual analog scale (VAS), which was anchored at 0 (definitely do not expect symptoms) to 100 (definitely expect symptoms). Perceived urge-to-cough was measured after each cough challenge using a modified vertical Borg scale (0-10, labeled from “not at all” to “extremely strong”). Prior beliefs about cough triggers were measured using the cough trigger inventory, an adapted version of the asthma trigger inventory (Ritz, et al., 2006), in which participants are asked about the frequency of cough when exposed to 32 potential cough triggers. Frequency of cough is rated on a 5-point Likert scale, labeled from “never” to “always”.

Procedure

The experiment took place over the course of two consecutive days. During the first day, participants provided informed consent, and subsequently performed the cough threshold task and trigger acquisition task in the lab. During the next day, participants completed the trigger generalization task, using an online survey.

Cover story

During the informed consent procedure, participants received information that they would participate in the validation of a novel allergy test, and that this “allergy challenge task” consisted of short allergen inhalation challenges, in which pictures of potential allergens would be shown on a screen in order to aid recollection of triggers.

Cough threshold task

Threshold testing was carried out to identify the lowest concentration of citric acid that elicited at least 3 coughs (C3 criterion). Testing was performed using a semi-randomized staircase procedure in accordance with cough assessment guidelines of the European Respiratory Society (Morice et al., 2007): in a first block, participants received randomized presentations of saline, 30 mM citric acid, and 100 mM citric acid. In a second block, participants received randomized presentations of saline, 300 mM citric acid, and 1 M citric acid. If C3 was not reached during block 2, participants performed an additional cough provocation using a 3 M citric acid solution. At the end of each trial, participants provided an urge-to-cough rating. Inter-trial intervals were 90 s, and participants were required to take a sip of water between trials. At the end of the cough threshold task, participants filled out the cough trigger inventory.

Trigger acquisition task

During trigger acquisition, participants received a random series of 20 unique pictures, drawn from two trigger categories of the stimulus set. Participants were counterbalanced so that half of the participants received exemplars from two similar categories (e.g., mammals and birds) and the other half received exemplars from categories that were conceptually less similar (e.g., birds and molds). Within each counterbalanced group, assignment of specific picture categories to CS+/CS- was random, cf. Table 2. Five seconds after stimulus onset, participants rated symptom expectancy. Subsequent inhalation trials were based on trigger

category membership: pictures from one category (CS+ category) were followed by inhalation of a C3 dose of citric acid (8/10 trials) or saline inhalation (2/10) trials. Pictures from the other category (CS- category) were always followed by saline inhalation. After inhalation, participants rated urge to cough.

Generalization task

One day after the trigger acquisition task, participants completed an online survey. In the online survey, participants were presented with the full 80-picture stimulus set. For each of the pictures in the 80-item stimulus set, participants indicated (a) if the picture had been featured in the lab-based task (forced choice: yes or no), and (b) if they would expect symptoms when confronted with this trigger (rated on a 0-100 scale anchored at 0 (definitely do not expect symptoms) and 100 (definitely expect symptoms)). At the end of the survey, participants were fully debriefed.

Data analysis

Data analysis was carried out in SPSS (version 23, IBM, Armonk, NY) using hierarchical linear modeling, implemented using Satterthwaite approximation for calculation of df and p-values. All models were determined a priori. Models for cough responses and urge-to-cough consisted of fixed effects of stimulus type (CS+ citric acid, CS+ saline, CS- saline), Trial (numeric), and Group (Control, Rhinitis), as well as their interactions, and a random intercept and random slope (Trial), and an unstructured variance-covariance matrix. Cough responses were log-transformed prior to analysis. For symptom expectancies during acquisition, the model consisted of main effects of stimulus type (CS+, CS-), Trial (numeric), and group (Control, Rhinitis), as well as their interactions, and a random intercept and random slope (Trial), and an unstructured variance-covariance matrix. Additional analyses were carried out including CS category similarity. Analyses of generalized trigger beliefs were carried out using analyses that included a random intercept model. Based on the

categories that were presented during acquisition, each of the pictures in the trigger stimulus set was coded creating a category of old and novel CS+ and CS- pictures, as well as generalization categories that were related to the CS+ category (G+), CS- category (G-), or unrelated to the CS categories (Gu); cf. Table 2 for an overview. Two sets of analyses were carried out: a first analysis tested generalization to novel exemplars, and was limited to CS exemplars. This analysis included main effects of stimulus type (CS+, CS-), Stimulus Novelty (old, new), CS category similarity, and Group, as well as their interactions. Generalization to novel trigger categories was investigated using a separate model, that included main effects of stimulus type (CS+, CS-, G+, G-, Gu) and Group, as well as their interactions. Models for trigger recognition (hits) were generalized (logistic) mixed models, which included main effects of CS type (CS+ vs CS-), CS category similarity, Group, and their interactions, and also included a random intercept. Analyses of false alarms were conducted separately for CS and G exemplars, and also included main effects of stimulus type (CS(CS+ vs CS-) or G(G+, G-, Gu) respectively), CS category similarity, Group, and their interactions, as well as a random intercept.

Results

Cough and urge-to-cough thresholds

Cough and urge-to-cough thresholds are presented in Table 3. Participants with allergic rhinitis and control participants did not show significant differences in cough or urge to cough thresholds, although C3 thresholds may have been higher in individuals with rhinitis compared to control participants (cf. Table 3). Four participants (2 control participants) did not reach the C3 criterion during threshold test.

Cough response and urge to cough during acquisition

Citric acid (CS+) trials resulted in a greater number of coughs compared to saline (CS-) trials ($t(792)=37.93$, $p<.001$). However, coughs in response to CS+ saline trials did not differ from CS- (saline) trials ($t(812)=0.83$, $p=0.999$), cf. Figure 1a). We did not observe differences in cough response between participants with allergic rhinitis and control participants ($F(1,72)=0.183$, $p=.670$). Finally, cough response to citric acid decreased with repeated provocations ($t(797)=-3.00$, $p=.003$), whereas no decrease in cough was observed for CS- (saline) trials ($t(152)=0.196$, $p=.845$).

For urge-to-cough, we observed similar effects, with greater urge to cough after citric acid compared to saline inhalation ($t(838)=44.40$, $p<.001$, cf. Figure 1b), and urge-to-cough after citric acid decreasing with repeated provocations ($t(839)=-3.24$, $p=.001$).

Acquisition of trigger beliefs

During trigger acquisition, symptom expectancies increased across trials for CS+ triggers but not for CS- triggers ($F(1,748)=49.395$, $p<.001$), and reaching a 19,3 difference [13.6-24.9], $p<.001$ at trial 10 (Figure 2a). Furthermore, this increase in symptom expectancies for CS+ triggers was stronger in the rhinitis group compared to the control group ($F(1,748)=6.549$, $p=.011$), but group differences between CS+ and CS- did not reach significance at trial 10 (Estimate=10.2 [-1.1-21.5], $p=.076$), (cf. Figure 2b),. Additional analyses including similarity between CS+ and CS- categories did not result in significant main or interaction effects of category similarity (all p 's $>.16$).

Generalization of trigger beliefs

Generalization to novel exemplars

In a first set of analyses, only expectancies to CS+ and CS- triggers were analyzed with CS Type (CS+ vs CS-), Stimulus Novelty (Old vs. New), CS Category Similarity (Similar vs. Dissimilar), and Group (Allergic Rhinitis vs. Control) as factors. Results showed increased symptom expectancy for CS+ compared to CS- exemplars ($F(1,1711)= 248,06$, $p<.001$), and

for old vs novel CS exemplars($1,1711)=8,91$, $p=.003$). The effect of CS Type was further qualified by an interaction with Category similarity ($F(1, 1711)=11.54$, $p=.001$): greater differentiation between CS+ and CS- exemplars was observed when CS categories were more similar. CS Type also interacted with Group ($F(1,1711)=6.64$, $p=.01$) showing stronger differentiation between CS+ and CS- exemplars in control participants compared to participants with rhinitis (cf. Figure 3). There were no other significant effects.

Generalization to novel categories

In a second set of analyses, we investigated responses to the full set of exemplars of both trigger categories encountered during acquisition (CS+ and CS-), as well as novel trigger categories (G+, G-, Gu). As shown in Figure 4, symptom expectancies for generalization categories G+ and G- were rated higher compared to CS- ratings, and lower compared to CS+ ratings, whereas Gu ratings did not differ from CS- ratings (main effect of trigger category $F(4,3483)=92.495$, $p<.001$). Trigger category ratings furthermore differed between groups (trigger category x Group interaction $F(4,3483)=12.288$, $p<.001$). Further exploration at the level of the individual trigger category showed no significant between-group differences, with the exception of Gu symptom expectancy, which was higher in participants with allergic rhinitis compared to control participants ($F(1,47)=6.095$, $p=.017$, cf. Figure 4). Moreover, linear generalization slopes (testing for differences in the linear trend comparing expectancies for CS-, G-, G+, CS+, Figure 4) were steeper for control participants compared to individuals with allergic rhinitis ($t(3468)=3.371$, $p=.001$).

Trigger recognition

Trigger recognition models included CS Type (CS+ CS-), CS Category Similarity (Similar vs. Dissimilar), and Group (Allergic Rhinitis vs. Control), as well their interactions. Analysis of hit rates showed that when participants had been shown dissimilar CS categories during acquisition, hit rate was greater for CS+ exemplars (.87 [0.81-.91]) compared to CS-

exemplars (.80 [.73-.86], $t(872)=1.979$, $p=.048$). When participants had received similar CS categories during acquisition, hit rate did not differ for CS+ (.76 [.67-.83]) and CS- (.81 [.73-.87]) exemplars ($t(872)=-1.352$, $p=.177$; CS Category Similarity X CS Type $F(1,872)=5.633$, $p=.018$). Analysis of false alarms (conducted separately for CS and G exemplars) did not return any significant results.

Discussion

Individuals with respiratory allergies typically develop beliefs about contingencies between triggers and symptoms. In this experiment, we mimicked this process by investigating acquisition of trigger-cough contingency beliefs using a trial-unique differential conditioning procedure. In addition, we investigated generalization of these beliefs along conceptual relationships between triggers. Replicating and extending previous work done in healthy participants, with CO₂ as an unconditioned stimulus (Janssens, et al., 2015), we showed that participants were able to use category information to predict contingencies between unique “allergens” and the occurrence of cough. During retention and generalization tests, our results showed that trigger-symptom contingencies generalized to novel CS+ trigger exemplars, as well as novel trigger categories.

Replicating these findings using citric-acid induced cough add to the ecological validity of the experimental task by increasing the relevance for the many conditions that include cough as a symptom. Furthermore, inclusion of participants with allergic rhinitis allowed us to test acquisition and generalization of symptoms in a population for whom real life trigger detection is an important task.

Interestingly, acquisition and generalization of trigger beliefs differed for participants with allergic rhinitis compared to control participants. Participants with allergic rhinitis showed faster acquisition of CS+ trigger beliefs. However, one day later, they showed less

differentiation between CS+ and CS- trigger categories, as well as more generalization to novel trigger categories, regardless of the similarity of GS and CS categories).

Group differences in the acquisition and generalization of symptom expectancies may be the result of differences in prior experience with allergens as symptom triggers. Research on fear learning has shown that prior expectancies or beliefs can facilitate acquisition and hampering extinction (Davey, 1995). Therefore, a priori cough beliefs related to allergic triggers may have facilitated acquisition and generalization in individuals with rhinitis. In a similar way, prior experiences with non-occurrence of symptoms in response to allergens in the control group may have caused latent inhibition (Lubow and Gewirtz, 1995; Vervliet, Kindt, Vansteenwegen, & Hermans, 2010), hampering trigger acquisition and generalization in this group. Furthermore, observed differences in cough sensitivity between participants with allergic rhinitis and control participants are unlikely to have caused differences in acquisition or generalization, due to CS+ citric acid inhalations being tailored to individual C3 thresholds, resulting in similar symptom experiences across both groups. Finally, the lack of group differences in trigger recognition data suggest that trigger generalization effects are not a result of a lack of perceptual discrimination between individual trigger exemplars or differences in category-based memories for trigger exemplars.

Similar to a previous experiment using similar methods (Janssens, et al., 2015), symptom expectancies and trigger recognition depended on the relationship between the categories that were used during acquisition. Retention and generalization of differential trigger beliefs was stronger when participants had been presented with more similar compared to dissimilar trigger categories during acquisition. Furthermore, the trigger recognition data suggest that this increased differentiation between symptom expectancies for similar CS categories may come at the expense of differentiation within a single trigger category.

Our findings suggest that category-based generalization may explain the poor correspondence between trigger beliefs and allergic reactivity to specific allergens that is observed in individuals with allergic conditions (Graif, et al., 2006; Janssens and Harver, 2015; Li, et al., 2000; Smith, et al., 2009). Furthermore, our observation that the relationship between CS+ and CS- categories has an impact on retention and generalization of symptom expectancies may lead to interventions that explicitly help individuals to differentiate between triggers and non-triggers. This could be achieved by changing the information that individuals with asthma receive from their health care providers, or by offering symptom differentiation training as part of an allergy management plan (Janssens, et al., 2015). Development and evaluation of these interventions has the potential to limit trigger generalization and improve quality of life for individuals with allergic conditions. Our current study is a first step on this path, as it highlights the difficulties associated with the acquisition of trigger beliefs, as well as a potential way to change generalization of trigger beliefs.

There are a number of limitations to the study. First, the investigation of category relations and generalization to novel trigger categories was restricted to specific categories of the stimulus set. For example, if participants received CS categories that were similar (e.g. flowers and molds), we could only test generalization to G's that were unrelated to the CS categories (e.g. mammals and birds).

Furthermore, the experimental design did not allow for inclusion of a pre-test of symptom expectancies for the trigger stimulus set, as presentation of the whole trigger set would have interfered with trigger recognition tests. The lack of a pre-test of symptom expectancies makes it more difficult to interpret the results of the generalization test, as

responses to GS exemplars can reflect both trigger generalization as well as pre-existing trigger beliefs.

A further limitation of our study is that we study differences in generalization after an acquisition task in which we observed group differences in learning. Although group differences in differential learning did not reach significance at the end of acquisition, these differences make it difficult to disentangle performance in the generalization task from differences observed during acquisition.

Our findings are further limited by the change of context and format of the generalization test, which was carried out online and not in the trial by trial “allergen challenge” format of the acquisition context. This is different from other studies that have typically investigated generalization under conditions of either continued pairing of the CS+ with the unpleasant outcome, or under conditions of extinction (similar context, but no unpleasant outcomes present). In the generalization test of the present study, we therefore only were able to test generalization of trigger beliefs, but not to test if these beliefs would change when participants were confronted with a lack of contingency between generalization triggers and unpleasant outcomes. This aspect of generalization, associated with lack of safety learning has been identified as a potential mechanism for generalization in individuals with anxiety disorders (Britton, Lissek, Grillon, Norcross, & Pine, 2011; Gazendam, Kamphuis, & Kindt, 2013). Given the large comorbidity between anxiety and allergic conditions (Chida, Hamer, & Steptoe, 2008; Lu et al., 2012) future extensions of research focusing on generalization and safety learning may be needed to further our understanding of generalized trigger beliefs.

A final limitation of our study is that is that participant diagnosis of allergic rhinitis was based on self-report, and not confirmed by physician evaluation or IgE tests. Our reliance on self-reported allergic rhinitis symptoms has the risk of only recruiting participants who are aware of their rhinitis, as well as potential misdiagnosis. A multi-country population-based

study confirms this risk, with about 15% of self-reported rhinitis being false positive and about 30% of participants with a lab-based diagnosis of rhinitis being previously unaware of their condition (Bauchau and Durham, 2004). This could have resulted in our group of participants with self-reported rhinitis diagnosis having stronger symptoms, as well as a higher number of triggers compared to the overall population of individuals with rhinitis – inflating differences between participants with rhinitis and control participants.

In conclusion, the results of the present study confirm the role of previously acquired conceptual knowledge in the acquisition and generalization of trigger beliefs, showing that trigger beliefs about novel allergens are easily acquired, and generalize to novel category exemplars as well as exemplars of categories that are similar to the ones that were presented during acquisition. Compared to control participants, participants with allergic rhinitis showed faster acquisition of trigger beliefs and greater symptom expectancies for novel trigger category exemplars. These findings suggest that personal relevance, or previous experience with allergy triggers may be crucial to determine the degree of trigger acquisition and generalization, although future studies will be needed to further explain which conditions may lead to specific patterns of generalization.

Our findings can help to understand the occurrence of inaccurate trigger beliefs, and its associated burden in individuals with allergic conditions, highlighting the role of conceptual knowledge and generalization in the development of inaccurate trigger beliefs. Finally, our results suggest that training individuals with allergic conditions to differentiate between triggers and non-triggers. Furthermore, differentiation training using triggers and non-triggers that are conceptually similar may help to increase the accuracy of trigger beliefs, although further research is needed to investigate its efficacy when applied in the context of allergy treatment.

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Tables

Table1: Characteristics of participants with rhinitis and control participants

Variable	Control Group		Rhinitis Group		t	p
	M	SD	M	SD		
Age	22.4	1.14	22.4	1.71	-0.104	0.918
Female (n, %)	19	86%	19	86%		
Cough Trigger Inventory (n=39)						
Psychological	0.130	0.181	0.185	0.223	0.856	0.397
Allergens	0.457	0.465	1.414	0.851	4.415	<.001
Exercise	1.050	0.605	0.930	0.755	-0.555	0.582
Irritants	1.533	0.627	1.508	0.632	-0.126	0.901
Infection	1.963	0.645	1.825	0.828	-0.586	0.561
Total	0.838	0.282	1.023	0.390	1.728	0.092
Note: Cough trigger frequencies are rated on a scale ranging from 0 (Never) to 4 (Always)						

Table 2: Trigger stimulus set and category relations

CS+ and CS- conceptually similar			
CS+	CS-	Gu	
Flowers	Molds	Birds, Mammals	
Molds	Flowers	Birds, Mammals	
Birds	Mammals	Flowers, Molds	
Mammals	Birds	Flowers, Molds	
CS+ and CS- conceptually dissimilar			
CS+	CS-	G+	G-
Flowers	Birds	Molds	Mammals
Molds	Mammals	Flowers	Birds
Birds	Molds	Mammals	Flowers
Mammals	Flowers	Birds	Molds
Note: G+: Generalization stimuli conceptually related with CS+, G-: Generalization stimuli conceptually related with CS, Gu: Generalization stimuli unrelated to CS+ or CS-			

Table 3: Cough and urge-to-cough thresholds in Rhinitis and Control groups

Threshold	Group	Reached	0 mM	30 mM	100 mM	300 mM	1000 mM	3000 mM	χ^2 (<i>p</i>)
C2	Control	22/24		2	2	11	7		3.042 0.3852
	Rhinitis	23/24		1	2	7	13		
C3	Control	22/24		1	3	12	6	0	9.43 0.0512
	Rhinitis	22/24		1	1	5	13	2	
C5	Control	13/24		0	3	2	8		7.405 0.06
	Rhinitis	11/24		1	0	5	5		
Cu	Control	24/24	5	8	6	4	1		1.641 0.8013
	Rhinitis	24/24	5	7	7	5	0		

Note: C2-C5-Cu: minimal dose eliciting 2 coughs - 5 coughs - urge to cough

Figure Captions

Figure 1: Cough response (panel a) and urge-to-cough rating (panel b) in response to saline and citric acid during acquisition phase.

Figure 2: Symptom expectancy in response to CS+/CS- trigger category exemplars during acquisition collapsed across both groups (panel a) and separate for Rhinitis and Control groups (panel b).

Figure 3: Symptom expectancies during generalization test for CS+ and CS- exemplars, depending on group membership and CS category similarity.

Figure 4: Generalization of symptom expectancies to novel trigger categories