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Memory and multitasking performance during acute allergic inflammation in seasonal allergic rhinitis

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Running head: memory and multitasking in rhinitis

Abstract

Background: In previous research patients with seasonal allergic rhinitis (SAR) showed poorer school and work performance during periods of acute allergic inflammation, supporting the idea of an impact of SAR on cognitive functions. However, the specific cognitive domains particularly vulnerable to inflammatory processes are unclear.

Objective: In the present study the influence of SAR on memory and multitasking performance, as two potentially vulnerable cognitive domains essential in everyday life functioning, was investigated in SAR patients.

Methods: Non-medicated patients with SAR (n=41) and healthy non-allergic controls (n=42) performed a dual-task paradigm and a verbal learning and memory test during and out of symptomatic allergy periods (pollen vs. non-pollen season). Disease-related factors (e.g., symptom severity, duration of symptoms, duration of disease) and allergy-related quality of life were evaluated as potential influences of cognitive performance.

Results: During the symptomatic allergy period, patients showed (a) poorer performance in word list-based learning ($p = .028$) and (b) a general slowing in processing speed ($p < .001$) and a shift in processing strategy ($p < .001$) in multitasking. Yet, typical parameters indicating specific multitasking costs were not affected. A significant negative association was found between learning performance and duration of disease ($r = -.451$, $p = .004$), whereas symptom severity ($r = .326$; $p = .037$) and quality of life ($r = .379$; $p = .015$) were positively associated with multitasking strategy.

Conclusions: Our findings suggest that SAR has a differentiated and complex impact on cognitive functions, which should be considered in the management of SAR symptoms. They also call attention to the importance of selecting sensitive measures and carefully interpreting cognitive outcomes.

Keywords:

psychoneuroimmunology; seasonal allergic rhinitis; learning and memory; multitasking; processing speed;

Acronyms:

ANOVA=analyses of variance, BMI=body mass index, HC=healthy controls, IgE=immunoglobulin-E, PRP=psychological refractory period, RQLQ-S=rhinoconjunctivitis quality of life questionnaire, RT=reaction time, RT1=reaction time in Task 1, RT2=reaction time in Task 2, S1=stimulus in Task 1, S2=stimulus in Task 2, SAR=seasonal allergic rhinitis, SOA=stimulus onset asynchrony, SD=standard deviation, VAS-SAR=visual analogue scales for SAR symptom severity, VLMT=verbal learning and memory task

Introduction

Seasonal allergic rhinitis (SAR), commonly known as hay fever, is an allergic inflammatory disease of the upper respiratory tract caused by hypersensitivity towards otherwise harmless allergens (e.g., pollen). Prevalence rates reach up to 23% making SAR one of the most prevalent chronic diseases in western populations (1,2). In addition to the classical symptoms of sneezing, itching, and nasal obstruction, patients frequently report marked declines in everyday life cognitive demands such as concentration, memory, and learning abilities (3,4). Such impairments are of significant relevance as they can have profound consequences for the individuals' quality of life as well as school or work performance (5–7). Lamb et al. (8) reported that employees suffering from SAR are unproductive for an average of 2.3 hours per typical work day during symptomatic allergy periods, resulting in an estimated cost of \$593 per year and employee. Further, school children suffering from SAR experience a higher risk of achieving lower grades in examinations, if those tests took place during pollen season (9).

However, allergies are still invariably trivialized by patients and in medical context (10) and studies investigating cognitive functioning underlying these complaints are rare. We recently demonstrated that patients with SAR showed an altered performance in low-demanding selective attention tasks (e.g., selecting task-relevant information while ignoring conflicting task-irrelevant information) (11). Interestingly, performance in selective attention was not impaired per se. Patients rather showed a general slowing of task processing, but also a stronger recruitment of cognitive control when adjusting behavior after an experienced conflict. This pronounced adjustment of performance might reflect a compensatory strategy, for example, in terms of increased mental effort or volitional control in response to the experienced conflict (e.g., increased conflict-triggered processing

selectivity) compared to healthy controls. However, human cognition is not a unitary concept but comprises various forms of cognitive processing, any conclusions and transfer of a SAR impact to more complex cognitive domains remains entirely elusive.

In the present paper we therefore aimed at extending the study of SAR impact on cognitive processing by focusing on more complex cognitive demands, such as memory and multitasking (i.e., managing two or more tasks at the same time). In a study by Marshall et al. (4) about 44% of patients reported memory problems during symptomatic allergy periods and showed a slower performance in a word-list based memory test compared to healthy controls. Likewise, children with SAR showed reduced learning performance in a computer-based simulation of a school lesson (12). Vuurman and colleagues (13) further showed that driving performance of symptomatic patients with SAR was significantly impaired especially when the patients had to perform a parallel memory task. Impairments in driving abilities were comparable to effects seen with a blood alcohol level of 0.05%. Wilken et al. (14) showed that allergic provocation results in significant slower reaction times in a multitasking-related divided-attention task. However, this effect might be influenced by an unspecific slowing of processing speed in patients, which has been described by our own group and others (11,15). Thus, it remains unclear whether SAR directly affects multitasking or whether SAR slows down cognitive functioning non-specifically.

To further elucidate the cognitive processes leading to performance impairments in SAR, the present study aims to investigate and discuss memory and multitasking functions (during and out of symptomatic allergy periods) as two specific cognitive domains that play a pivotal role in most day-to-day real life task performances. Moreover, the impact of specific allergy-related characteristics (i.e., symptom severity, duration of the symptomatic period, rhinitis-related quality of life, and duration of disease in years) on cognitive performance was evaluated. In order to target the specific underlying processes, we implemented experimental paradigms that allow a careful examination of parameters indicating multitasking costs (e.g., 16,17) and the differentiation of learning performance from memory effects.

Methods

Patients

A total of 41 patients with SAR (21 males, M_{age} 24.1 (SD 3.3) years) and 42 healthy (20 males, M_{age} 24.4 (SD 3.1) years), non-allergic controls were recruited for the study. SAR was diagnosed by an allergist and considered to be confirmed by a positive skin prick test for at least one grass or tree pollen and/or elevated total immunoglobulin-E (IgE) levels (IgE > 100 IU/ml serum). All patients were off allergy medication (i.e., systemic or topical antihistamines, corticosteroids, or mast cell stabilizers) for at least seven days prior to testing, and 73% of patients fully stopped anti-allergic medication. Patients experienced a transient exacerbation of SAR symptoms after stopping anti-allergic medication (personal reports, data not shown) leading to moderate to severe SAR in all SAR patients (mean VAS-SAR score = 369; see Table 1). Short-time aggravation of allergic symptoms was intended since a strong and fully developed allergic reaction is required to study the effect of allergic inflammation on cognitive function. Patients with current or recent immunotherapy were excluded from the study. Further, patients with positive testing to perennial allergens (i.e., dust mite and cat dander) and a history of allergy symptoms related to perennial allergens were excluded. As a control group, non-allergic participants with no history of atopic disorder were investigated. Participants with other inflammatory or infectious disorders, psychiatric or central nervous system diseases or visual or auditory disabilities were excluded from the experiment. The study was approved by the ethics committee of the Technische Universität Dresden (EK 261072011) and written informed consent was obtained from all participants prior to inclusion. Participants received 60 Euro compensation for study participation.

Study design

In a longitudinal design, both experimental groups were studied during a symptomatic allergic period (pollen season, March-October 2012; “on-season”) and during a non-symptomatic period (non-pollen season, November 2012 – February 2013; “off-season”). Patients with SAR were included in the experiment after at least two weeks of moderate allergic symptomatology (rhinorrhea, sneezing, nasal congestion, red or watery eye). Patients had to be free from any allergy-related symptoms for at least 2 weeks prior to off-season testing to ensure subsiding of inflammation. To prevent possible sequence effects, first testing condition (“on-” vs. “off-season”) was balanced across participants, and a minimum time interval of three months between the two test conditions was defined. To control for

allergy-independent seasonal effects (climate, shorter day-light periods) assignment to testing condition in the control group was semi-randomized with test sessions during winter time being automatically classified as “off-season”. The study was embedded in a larger project assessing psychological and psychiatric outcomes of seasonal allergic rhinitis (10).

Assessment of allergy-related factors and symptom severity

Symptom severity and symptom-related impairment of everyday life quality were assessed via visual analogue scales (VAS-SAR) and via the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ-S, (18)). The RQLQ-S consists of 28 items on seven domains (nasal symptoms, ocular symptoms, general symptoms, sleeping disorders, practical problems, limitations of activity and emotional disorders) with scores ranging from 0 ('not impaired at all') to 6 ('severely impaired'). Overall RQLQ-S score was calculated from the mean values of the 28 items. Psychometric properties of the RQLQ-S indicate good internal consistency ($\alpha = 0.93$) and reliability (intraclass correlation coefficient = 0.97) (18). In addition, duration of SAR (in years) and duration of acute SAR episode (e.g., number of days with SAR symptoms prior to on-season testing) were evaluated via patients' self-report and a symptom diary.

Memory task

The verbal learning and memory task (VLMT) (19), a German adaptation of the Rey Auditory verbal learning task (RAVLT) measures functionality of verbal declarative memory and consists of a Learning List A and an Interference List B with each consisting of 15 semantically independent words. List A was presented five times (Trial 1-5) via headphones and participants were instructed to recall all words they remember after each sequence. The cumulative number of learned and correct remembered words from Trial 1 to 5 is defined as learning performance. Afterwards, List B was presented and prompted. Following recall of List B, participants were asked to recall List A again (Trial 6), which is defined as the immediate recall performance. After a delay of 30 minutes participants were asked to recall List A (Trial 7) which represents delayed memory performance. To control for baseline values, immediate and delayed performance scores were calculated as the difference of correct words between Trial 5 and 6 and Trial 5 and 7, respectively. A different set of words in List A was used in each testing session to prevent learning effects.

Multitasking

To assess multitasking performance, a typical dual-task paradigm was adopted (e.g., 16,20) that allows for testing the degree of simultaneous task processing and inter-task coordination. Participants performed two speeded choice reaction tasks (i.e., a single-digit categorization in Task 1 and a high vs. low tone discrimination in Task 2). Stimuli were presented successively with varying temporal intervals (i.e., stimulus onset asynchrony, SOA, of 85, 200, or 1000ms), which determined the extent of simultaneous task processing. Participants were instructed to first respond as quickly and accurate as possible to the visual stimulus of Task 1 (S1; i.e. the digits 1-9, except for 5) with index and middle finger of the right hand, and only subsequently respond to the auditory stimulus of Task 2 (S2; i.e., high tone of 900Hz vs. low tone of 350Hz) with the index and middle finger of the left hand. Reaction time and error percentage of both tasks were used as indicators of dual-task performance. Typical performance pattern in this dual-task paradigm are large performance costs in Task 2 (RT2 and error) when both tasks are performed simultaneously (short SOA). These dual-task costs decrease when the temporal delay between both tasks increases (long SOA). Therefore, quality of multitasking can be obtained in the differences of T2 performance (RT2) at short versus longer SOAs, an effect that is commonly referred to as the psychological refractory period (PRP) effect (17,21). At the same time, performance in Task 1 is usually unaffected by variations in the temporal task overlap, due to the instructed task prioritization. The stimulus presentation and data recording were implemented using Presentation software (Version 0.71; Neurobehavioral Systems, Inc., Albany, CA, USA).

Data analysis

In order to evaluate changes in memory performance across the two testing sessions, a series of two-way analyses of variance (ANOVAs) with the between-subject factor *Group* (patients vs. healthy controls) and the within-subject factors *Season* (on-season vs. off-season) was conducted for the number of correctly reported words, immediate, and delayed recall, respectively. For significant *Group x Season* interactions on a $p < .05$ level, post hoc analyses via independent *t* tests were applied to further compare group performance within a particular season and paired *t* tests to evaluate performance differences within one group across testing sessions. In the case of multiple comparisons due to interaction effects, *p* values were Bonferroni-corrected. For dual-task performance, a series of three-way ANOVAs with the factors *Group*, *Season* and *SOA* (85ms vs. 200ms vs. 1000ms) was

conducted for mean RT and percentage of errors in Task 1 and Task 2 separately. For RT analysis only, errors and RTs differing more than 2.5 SD from each individual's condition-specific mean (8.5%) were excluded from analyses in both tasks. All statistical tests were performed at a 0.05 level of significance. To explore associations of dual-task and memory performance and specific allergy characteristics, Pearson correlations between the cognitive outcome measures and allergy characteristics were conducted. Analyses were conducted using SPSS 21.0 for Windows (SPSS Inc., 2009).

Results

Demographic and allergy characteristics

Demographic and allergy characteristics are displayed in Table 1. Groups did not differ regarding to age, sex, and BMI. As expected, patients showed significant worsening in symptom severity and quality of life (RQLQ-S) during on-season testing when compared to off-season testing.

Memory task

As depicted in Figure 1 analyses of the memory task revealed a significant *Group x Season* interaction, $F(1,81) = 9.084$, $p = .003$, $\eta^2 = .10$ in learning performance. Post hoc *t* tests showed that during on-season, patients with SAR learned significantly fewer words when compared to non-allergic control participants (mean of correct words: 60.15 for SAR vs. 63.55 for HC), $t(81) = -2.51$, $p = .028$ or when compared to the off-season period (mean of correct words: 60.15 for on-season vs. 62.83 for off-season), $t(40) = -2.98$, $p = .010$. No main effects for *Season* $F(1,81) = 1.87$, $p = .17$, $\eta^2 = .02$, or *Group* could be found $F(1,81) = 1.52$, $p = .22$, $\eta^2 = .02$. ANOVA for immediate memory showed a significant main effect for *Group* with poorer performance in patients (Mean loss: .890 for SAR vs. .181 for HC), $F(1,81) = 6.69$, $p = .012$, $\eta^2 = .076$, but no *Season* effect or *Group x Season* effect (all F s < 1). A similar pattern was observed for the delayed performance with a significant *Group* effect (Mean loss: .793 for SAR vs. .202 for HC), $F(1,81) = 7.97$, $p = .006$, $\eta^2 = .09$, but again, no *Season* or *Group x Season* effect (all F s < 1). Post hoc *t* tests for the observed main *Group* effects in memory differences for immediate memory ($p = .028$, one-tailed) and delayed recall ($p = .017$, one-tailed) between groups only reached significance during on-season testing and not during off-season testing (p s > .075).

Dual-task

Reaction time

Dual-task data are presented in Figure 2 and Table 2. Dual-task costs are examined in Task 2 (17). For all participants, we found that RT2 decreased with longer SOA (992ms, 890ms, and 611ms, for SOA 85ms, 200ms, and 1000ms, respectively), reflecting the usual PRP effect, $F(2,162) = 1002.84$, $p < .001$, $\eta^2 = .93$. Most importantly, these dual-task costs did not differ between groups and were unaffected by pollen season ($F_s < 1$). In the on-season testing, however, patients showed substantially reduced processing speed (942ms) compared to healthy controls (753ms), $t(81) = 4.55$, $p < .001$. In addition, patients responded 111ms slower in on-compared to the off-season, $t(81) = 3.63$, $p = .001$. Together, this effect resulted in a *Group* $\times$ *Season* interaction on RT2, $F(1,81) = 18.88$, $p < .001$, $\eta^2 = .19$ (see Figure 2) and explains the overall performance slowing for patients compared to healthy controls, $F(1,81) = 10.66$, $p = .002$, $\eta^2 = .12$. The main effect of *Season* did not reach statistical significance, $F(1,81) = 3.33$, $p = .072$, $\eta^2 = .04$.

In Task 1, the interaction effect for *Season* $\times$ *Group* was also observed, $F(1,81) = 14.78$, $p < .001$, $\eta^2 = .15$. Again, in the on-season, patients responded significantly slower (958ms) than healthy controls to presented targets (741ms), $t(81) = 4.46$, $p < .001$. Patients with SAR were also substantially slower in the on-season compared to the off-season (120ms), $t(40) = 3.02$, $p = .004$. The significant threefold interaction of *SOA* $\times$ *Season* $\times$ *Group*, $F(2,162) = 5.39$, $p = .005$, $\eta^2 = .06$, demonstrates that the season-dependent RT1 slowing for patients was not unspecific but was most pronounced at longest SOA (see Figure 2, upper right panel). This pattern suggests SAR-specific changes in dual-task processing. An additional slope analysis confirmed the significant steeper increase in RT1 with increasing SOA in patients compared to healthy controls during on-season (199ms vs. -45ms), $t(81) = 4.23$; $p < .001$, which could not be shown during off-season, $t(81) = 1.30$, $p = .20$. The main effect of *Season* was not significant, $F(1,81) = 1.12$, $p = .29$, $\eta^2 = .01$.

Error rates

Analyses of error rates for Task 1 and Task 2 revealed only a main effect of *SOA* in Task 1 (85ms, 3.00%; 200ms, 2.37%; 1000ms, 2.31%), $F(2,162) = 4.01$, $p = .02$, $\eta^2 = .05$ and Task 2 (85ms, 4.22%; 200ms, 4.29%; 1000ms, 3.51%), $F(2,162) = 5.35$, $p = .006$, $\eta^2 = .06$, respectively (all other $ps \geq .17$).

Correlational analysis

To further explore the relationship between changes in cognitive functioning and allergy-related factors, a correlational analysis was performed for the observed effects in memory and dual-task. To obtain a marker of general season-dependent response slowing in the dual-task we calculated differences in RT1 (RT1 response slowing) and RT2 (RT2 response slowing) between on-season and off-season testing. Further, the increase in RT1 from short to long SOAs (slope) during on-season was computed reflecting the strategic response slowing at long SOAs. Pearson correlations were calculated for the allergy-related factors symptom severity, number of days with symptoms, rhinitis-related quality of life (RQLQ-S), and duration of disease in years. Pearson correlations revealed a significant negative association between RT1 slope in dual task and symptom severity ($r = .326$; $p = .037$) as well as RQLQ-S scores ($r = .379$; $p = .015$). Further, a negative association of number of correct reported words in the VLMT and duration of SAR in years ($r = -.451$; $p = .004$) was found. There were no further associations of task performance with allergy-related features. Results are displayed in Table 3.

Discussion

The present study investigated the impact of acute allergic processes in SAR on two cognitive domains relevant for day-to-day cognitive performance, e.g., memory and multitasking. We demonstrated that when being exposed to allergens, patients with SAR show a poorer learning performance during on-season and moreover, a worsening in immediate and delayed memory. With respect to multitasking, firstly, a general slowing in processing speed during on-season was demonstrated in participants with SAR. Secondly, patients did not show dual-task specific impairments, as we did not find differences in dual-task costs (PRP effect; e.g., large performance costs in RT2 and errors when performing two tasks simultaneously) between patients and healthy controls. However, we observed a distinct response pattern in patients that suggests a shift in strategic dual-task *processing*. Finally, regarding the influence of allergy characteristics, symptom severity and worsening in rhinitis-related quality of life were positively associated with dual-task strategy and a long duration of disease was negatively associated with learning performance.

As hypothesized, patients with SAR experienced difficulties in learning and memory during periods of allergic inflammation. Particularly, learning performance as reflected by the total number of learned words over repeated learning trials was impaired during on-season compared to healthy

control participants. This result is in line with previous studies reporting slower learning rates and poorer learning performance in patients using experimental settings and real life observations (4,13,22,23). Additionally, patients showed a higher loss of words in immediate and delayed recall, reflecting an influence of SAR on memory function, that were especially pronounced during on-season testing. This is an important finding, as it confirms and extends previous reports of (partial) deficits in recall performance (3). It should be noted, however, that effects observed in our study are small, and interpretations in terms of inferred clinical relevance of memory decline in SAR should be handled with care.

The mechanisms contributing to learning deficits are rather speculative. In the present study, the observed deficits in learning and memory were not associated with symptom severity and quality of life suggesting that other factors than the experience of stressful and irritating allergic symptoms (e.g., the effects of inflammatory cytokines as described further below) may be responsible for cognitive impairment. This idea is supported by pharmacological studies showing that antihistaminic treatment results in symptom relief but does not eliminate memory problems (13,22). Further, learning deficit was positively associated with a long duration of disease, suggesting that cognitive impairments may accumulate over years, which highlights the potential relevance of a repeated allergic challenge on cognitive performance. Alternatively, allergic manifestation of the disease may interact with sensitive periods of cognitive development leading to a more pronounced cognitive impairment in participants with a long allergic history. It is important to note, however, that these ideas are highly speculative and extensive research is needed to examine the effect of allergic stimulation on cognitive functioning.

The underlying mechanisms of allergy-related effects on learning and memory are still unclear. Sleep deficits, mood disruption, impaired well-being due to medication or allergy symptomatology, as well as central nervous effects of inflammatory mediators such as cytokines or histamine released during allergic inflammation may play an important role (24–26). For example, cytokines have been found to act on brain functions by passing the blood brain barrier or via vagal nerve stimulation (27,28). After passage into the brain, cytokines can interact with different brain regions such as the anterior cingulate cortex or the prefrontal cortex (28–31). These neuronal projections play a pivotal role in cognitive functions (32,33). Studies using endotoxin challenge or cytokine treatment showed that increased levels of pro-inflammatory cytokines (e.g., IL-6 and TNF- α) were associated with decreased memory performance, processing speed, and motivation (26,34–36). Histamine as an

effective central neurotransmitter is also associated with cognitive functioning, emotion, and arousal (37). Most recent data also suggest that peripheral histamine may affect hippocampal activity which is known to play an important role in learning and memory (38). Although the underlying mechanisms are still elusive, it has been proposed that peripheral histamine may impact central histaminergic neurotransmission and hypothalamic activity via the circumventricular organs that lack a blood brain barrier or via activation of negative feedback mechanisms of central histamine release (39). However, studies investigating this immuno-neuronal relationship in clinical conditions are scarce.

In contrast to our expectations, we did not find multitasking ability in patients to be different from healthy controls. Their capacity to manage the processing of two tasks simultaneously is comparable in its nature to healthy participants. It is important to note, however, that SAR did affect dual-task *performance* in our study, which is discussed later in detail. In addition, patients showed a slowing of processing speed during on-season as indicated by longer reaction times independent of the task condition in both tasks. This finding is in line with previous studies reporting slower reactions in patients with SAR (11,15). Importantly, this unspecific slowing might interfere with the measurement of other specific cognitive domains. It is possible, that previously reported deficits in multitasking impairments seen in real life settings or more unspecific laboratory paradigms may derive from detriments in general cognitive processes that contribute to task performance (e.g., unspecific slowing of processing speed). Therefore, it seems of major importance to use cognitive measures that allow for untangling multitasking-specific processes from general processing impairments.

Moreover, despite comparable multitasking performance costs in the dual-task paradigm, patients demonstrated season-dependent alterations in *performing* the two tasks. During on-season testing, response to the prioritized task (Task 1) was slower the larger the temporal delay (SOA) was to the additional task (Task 2). It seems, as if patients “waited” with their response to Task 1 until the response for Task 2 was ready to be initiated and then group both responses. Although the present data lack statistical proof of such a grouping strategy¹, the result pattern might reflect either an attempt of compensatory strategy easing task performance, or the inability to follow the task instruction of responding firstly and without delay to Task 1. The possibly strategic slowing of prioritized task processing (RT1) was associated with symptom severity and rhinitis-related quality of life. This might

¹ A grouping strategy is indicated by high percentages of small inter-response intervals (IRI) between response in Task 1 and response in Task 2. Differences in the percentage of grouped responses (e.g., IRI < 100ms) between SAR (9.0%) and control group (7.7%) during on-season were not significant, $t(81) = .335$, $p = .739$.

indicate that the subjective awareness of allergy symptoms might indicate a shift in processing strategy. Compensatory strategies (e.g., by showing higher effort during task processing) to achieve performance levels comparable to healthy populations have previously been shown (15). In a prior work we could demonstrate changes in the context-dependent adjustment of attentional control, which might function as a compensatory strategy to cover impairments in attention caused by SAR (11). Furthermore, animal studies provide evidence that mice prefer the least stressful and anxiogenic strategy of solving the Morris Water Maze (i.e., an experimental design to assess spatial learning and memory in an uncomfortable environment) in states of acute inflammation (24). Hypothetically, the present alterations in dual-task performance, seen as strategic shifts in processing, might also be less stressful and exhausting for patients by easing the task execution (for similar strategic shifts in dual-tasking see for example, (40)). However, it is important to note that these considerations are highly speculative. Additional research is necessary to further clarify whether altered cognitive processing in patients with SAR reflects a conscious and adaptive strategy to maintain high performance levels also under distressing circumstances such as an ongoing suffering from allergic symptoms or alternatively, whether it reflects allergen-induced activation of distinct immuno-neural networks (e.g., sickness behavior).

In summary, our data indicate that SAR is linked with specific deficits in memory and multitasking during periods of acute allergic inflammation that may contribute to impaired everyday life performance. We could demonstrate significant impairments predominantly in learning ability as well as in processing speed. This should be particularly considered in the context of school and work productivity, where the impact of SAR is still underappreciated. Equally important is the finding that multitasking performance in patients is not characterized by differences in typical dual-task costs. Rather, general slowing of processing speed as well as changes in processing strategies may reflect major contributors to poorer everyday life performance seen during allergic reactions. Further research should consider the complexity of cognitive changes in allergic diseases and carefully select measures and paradigms to not misinterpret already observed effects. Detailed knowledge which specific cognitive domains are impaired and which motivational or strategic factors might influence the extent of impairments is important as it crucially influences patients functioning and well-being in work and family life. To better specify the allergy-related immunological components, other inflammatory conditions than allergy (e.g. chronic TH1 inflammatory diseases) and their impact on different cognitive domains should be investigated. Further, the implementation of additional subject groups treated with

specific anti-inflammatory substances may help to clarify which aspects of altered cognitive functioning in allergic patients are due to the allergic inflammatory condition, e.g. sickness behavior, and which represents a “learned” compensatory behavior.

Considering the current findings (supplemented by suggested future research approaches) in clinical practice may lead to improvements in therapeutic strategies and interventions. Raising the awareness that impaired cognitive performance may be a frequent symptom of an ongoing allergic inflammatory process may help patients to better deal with learning and memory problems during acute allergic episodes. SAR treatment including short memory and learning training programs compatible with everyday life activities may improve cognitive functioning in selected allergy patients. This may help to delineate new approaches for treating the allergic patient instead of treating the allergic symptoms and may empower patients to optimally deal with the broad range of burdening SAR complaints.

Author Contributions

KT is responsible for the study concept and design, conducted the statistical analyses and wrote the manuscript. ABK is principle investigator, responsible for study design and contributed substantially to the interpretation of the data. FP is responsible for study design and contributed substantially to the interpretation of data. JS contributed substantially to the interpretation of the data. RF guided the statistical analyses and contributed substantially to the interpretation of the data. All authors approved the final version of the manuscript.

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Table 1: Demographic and allergy characteristics.

Characteristics	SAR Patients (n = 41)	Healthy Controls (n = 42)	Statistics
Age in years, mean (SD)	24.12 (3.3)	24.43 (3.1)	$p=.662$
Male, n (%)	21 (51.2)	20 (47.6)	$p=.876$
BMI, mean (SD)	22.93 (2.5)	22.58 (2.0)	$p=.473$
Days with allergy symptoms, mean (SD)	16.45 (11.5)		
SAR duration in years, mean (SD)	12.5 (5.8)		
Range	3 - 27		
SAR patients (n = 41)			
Allergy Characteristics:	On-season	Off-season	Statistics
Symptom severity (VAS-SAR)	369 (170)	43.6 (27.2)	$p<.001$
RQLQ-S	68.0 (24.9)	3.0 (3.9)	$p<.001$

Note. SAR, Seasonal allergic rhinitis; BMI, Body mass index; RQLQ-S, Rhinoconjunctivitis Quality of Life Questionnaire

Table 2. Mean error rates (%) for Task 1 and Task 2 for both groups (SAR vs. control group) and test sessions (on-season vs. off-season) as a function of the different stimulus onset asynchronies (SOAs), respectively. Standard errors of means (SE) are displayed in parenthesis

		SAR Patients (<i>n</i> = 41)		Healthy Controls (<i>n</i> = 42)	
SOA		On-Season	Off-Season	On-Season	Off-Season
Error in Task 1	85ms	3.74 (.61)	2.86 (.53)	2.34 (.60)	3.05 (.53)
	200ms	3.62 (.75)	2.06 (.34)	2.34 (.75)	1.45 (.34)
	1000ms	3.20 (.88)	1.52 (.34)	2.23 (.87)	2.27 (.34)
Error in Task 2	85ms	5.03 (.67)	3.84 (.62)	3.93 (.66)	4.08 (.61)
	200ms	5.07 (.74)	3.80 (.64)	4.64 (.73)	3.64 (.63)
	1000ms	4.28 (.66)	3.34 (.55)	3.36 (.65)	3.06 (.54)

Note. SAR, Seasonal Allergic Rhinitis.

Table 3. Pearson correlations of dual-task and memory performances with allergy-related factors for patients with SAR during on-season testing.

	Symptom severity at test day		Number of days with symptoms		RQLQ score		SAR duration in years	
RT1 response slowing	<i>r</i> = .130	<i>p</i> = .418	<i>r</i> = .209	<i>p</i> = .208	<i>r</i> = -.060	<i>p</i> = .709	<i>r</i> = .049	<i>p</i> = .768
RT2 response slowing	<i>r</i> = -.068	<i>p</i> = .672	<i>r</i> = .150	<i>p</i> = .369	<i>r</i> = -.268	<i>p</i> = .090	<i>r</i> = .009	<i>p</i> = .956
RT1 slope	<i>r</i> = .326*	<i>p</i> = .037	<i>r</i> = .238	<i>p</i> = .150	<i>r</i> = .379*	<i>p</i> = .015	<i>r</i> = .040	<i>p</i> = .807
Number of correct words in VLMT	<i>r</i> = -.162	<i>p</i> = .312	<i>r</i> = .127	<i>p</i> = .447	<i>r</i> = -.195	<i>p</i> = .222	<i>r</i> = -.451*	<i>p</i> = .004
Delayed recall performance in VLMT	<i>r</i> = .099	<i>p</i> = .537	<i>r</i> = .085	<i>p</i> = .612	<i>r</i> = .291	<i>p</i> = .064	<i>r</i> = -.065	<i>p</i> = .696

**p* < .05; RQLQ-S, Rhinoconjunctivitis Quality of Life Questionnaire; RT1, Reaction Time in Task 1; RT2, Reaction Time in Task 2; VLMT, Verbal Learning and Memory Test.

Figure Capture

Figure 1. Total number of correct remembered words in VLMT in Trial 1 to 5 for patients with SAR and healthy controls at both testing sessions (on-season vs. off-season). Error bars reflect standard errors of mean. SAR, seasonal allergic rhinitis; HC, healthy controls; VLMT, Verbal Learning and Memory Test **p* < .05.

Figure 2. Response Times (RTs in ms) depending on SOA for Task 1 (RT1) and Task 2 (RT2) for patients with SAR and healthy controls at both testing session (on-season vs. off-season). Error bars reflect standard errors of mean. SAR, seasonal allergic rhinitis; HC, healthy controls; SOA, Stimulus Onset Asynchrony; ** *p* < .01; *** *p* < .001.



