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Idiopathic Environmental Intolerance: A Treatment Model

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Idiopathic environmental intolerance (IEI) refers to a health condition characterized by the presence of multiple symptoms in different organ systems in response to a variety of environmental cues, such as chemical exposures, electromagnetic radiation, infrasound from windmill farms, (parts of) buildings, foods, etc. Typically, the symptoms arise in response to triggers and at dosages that do not cause symptoms in the majority of people, and no clear link with any physiological dysfunction can be found. The condition varies in a dimensional way from very mild, for which no medical help is sought, to very disabling, compromising normal life. The condition is controversial, but several indications strongly suggest that the symptoms result from nocebo mechanisms. Currently, different psychological treatments are explored, but they are generally not based on a clear understanding of the aetiopathological mechanisms and the treatment effects are not well documented. In the present paper, we describe a treatment protocol based on a comprehensive explanatory model of IEI. The goal is to contribute to standardized, mechanism-based treatments as a basis for more systematic treatment studies.

Idiopathic Environmental Illness: What Is It?

For 20 years, Tom has worked as a technical assistant in a chemical plant that produces plastics. He is mildly allergic to triethylamine (TEA and TEA-HCL), a colorless liquid with a fish-like odor that is used in the plant. In allergic persons, contact with triethylamine can irritate the skin and eyes, with possible eye damage, and inhaling it can irritate the lungs. At high exposures, it may cause pulmonary edema, a medical emergency. So, Tom is very careful to avoid any contact with the product. Nevertheless, across the years he started to develop somatic complaints in response to an increasing variety of substances, such as household cleaning products, fresh paint, pesticides and herbicides, smoke, diesel exhausts, perfumes and deodorants, washing products and soaps, etc. Typical complaints include tiredness, dizziness, heart pounding, lightheadedness and concentration problems, gastro-intestinal symptoms, burning eyes, weird sensations in the mouth, and a few others. At some point, he had a sudden exacerbation of symptoms that brought him into the emergency unit, where he underwent various medical examinations, but no physiological abnormality could be found. Tom is convinced that triethylamine is the causal factor that has sensitized him to an increasing number of products. However, toxicologists and occupational physicians tell him that his large variety of symptoms in response to such a wide range of chemically unrelated products cannot be explained by it. He has been on sick leave for months but returned to work after special working conditions have been offered. He considers suing the company, but he finds no expert support for his case. He feels abandoned by the health care system and is hopeless. Because triggers of his symptoms are abundantly present everywhere, his life has turned into a hell.

Tom is a prototypical case of multiple chemical sensitivity (MCS), one type of idiopathic environmental intolerance (IEI).[1] Other types are, first, hypersensitivity to electromagnetic fields (EMF), when symptoms are attributed to power lines, remote controllers, mobile phones and their relay stations, radios, computers; and, second, infrasound hypersensitivity (IHS), when symptoms are attributed to low frequency noise, such as that produced by wind turbines. A number of other health problems, such as sick building syndrome and several food and alcohol intolerances, are most likely other instances of IEI because of the many shared characteristics (Van den Bergh, Brown, et al., 2017). Typical for IEI is that (a) no link between self-reported symptoms and any objective organ pathology or dysfunction can be established; (b)

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[1] A very recent position paper suggested an alternative term, "symptoms associated with environmental factors (SAEF)" (see Haanes et al., 2020).

heterogeneous symptoms appear in response to a variety of environmental sources that are unrelated in a physical or chemical sense, and at intensities well below generally accepted thresholds for harmfulness; (c) perceptual hypersensitivity cannot be demonstrated in well-controlled blinded exposure studies; (d) consistent evidence points to the involvement of psychological processes, such as hypervigilance to potential environmental sources and bodily responses, somatic attributions, and enhanced emotional responding to the purported sources of the symptoms (cf. Baliatsas, et al., 2012; Lacour et al., 2005). In addition, evidence suggests a large symptom overlap with somatoform disorders and other functional syndromes, such as chronic fatigue syndrome, fibromyalgia, and war syndromes (e.g., Bailer, et al., 2005; Reid et al., 2001). Up until now, no consensus exists among health care professionals regarding an adequate evidence-based treatment of patients suffering from IEI.

In this paper, we aim to describe a structured program to treat these patients. This program is based on a theoretical model of IEI (Van den Bergh, Brown, et al., 2017) as well as on clinical experiences in the treatment of IEI patients. First, we will briefly describe critical processes implied in the clinical features of these patients, and, second, some important diagnostic elements. Next, we will elaborate more extensively on the general treatment rationale and the different steps in the treatment process.

Understanding IEI: Central Mechanisms and a Comprehensive Model

Previously we have summarized and evaluated the evidence to understand MCS, EMF, and IHS (Van den Bergh, Brown, et al., 2017). This analysis showed that symptoms critically depend on expectancy: if triggers are perceivable during exposures, symptoms emerge, but if they are hidden but present, they do not. In addition, experimental procedures that create expectancy also induce symptoms in the absence of the assumed harmful stimuli. In other words, there is convincing evidence that a nocebo effect is strongly involved in the development and maintenance of IEI symptoms. A nocebo effect, the opposite of a placebo effect, refers to worsening of one's health as a result of mechanisms related to expectancy. The problem is then twofold: first, to understand how nocebo mechanisms can create the experience of symptoms as caused by the environmental triggers, and second, how we can interfere with these processes such that the patients no longer experience symptoms in response to the trigger stimuli, and can return to normal life. We have recently proposed a model of IEI that builds upon a predictive processing perspective on symptom perception (Edwards et al., 2012; Van den Bergh, Witthöft, et al., 2017) and that integrates the available empirical evidence on crucial mechanisms involved in symptom development and chronicity in IEI (Figure 1). We briefly summarize the essence of the model here. For an elaborated explanation, see Van den Bergh, Brown, et al., 2017.

According to this model, the generation of symptoms in response to environmental triggers implies two processes: first, an (automatic) perceptual-inferential process involving the integration of prior expectancies and the currently available sensory input generates the experience of symptoms. Prior expectancies (or prior beliefs) should not be equated with explicit conscious expectations, but as neural activity representing previous symptom episodes that are automatically activated by the brain in response to cues and contexts associated with symptom episodes. Neural distributions representing actual somatic input will interact with prior beliefs at multiple hierarchical processing levels, creating prediction errors that are propagated through the brain in a prediction error minimization process. It is assumed that the experience of symptoms emerges when the overall level of prediction error cannot be further reduced. Importantly, the relative impact of prior beliefs versus actual somatic input on the eventual symptom experience depends on reliability parameters of these neural distributions (precision). This means that the eventual symptom experience may reflect highly precise prior expectancies more closely than (less precise) actual somatic input. In the extreme case, symptoms may completely be determined by expectancies. Multiple cognitive and physiological sources may contribute to this process (e.g., low pCO_2 levels, allergic reactions, stress-related physiological arousal, depressive mood and anxiety may generate somatic sensations at first, while expectancy-based processes may subsequently take over and foster the development of chronic somatic symptom distress).

Second, mechanisms of causal perception, such as spatial and temporal relationship between environmental cues and symptoms, the novelty and intensity of cues, their consistency with one's own actions, beliefs, and worries contribute to the experience of a strong causal connection between environmental stimuli (e.g., odors, chemicals, Wi-Fi radiation, sounds) and the symptoms, thereby creating IEI triggers (see Van den Bergh, Brown, et al., 2017, for further elaborations).

Experimental studies and clinical observations suggest that associations between symptoms (stage 1, Figure 1) and environmental stimuli can be formed via different processes: classical conditioning (with or without explicit knowledge of this association), attribution processes (triggered by the urge to retrospectively make sense of otherwise unexplained somatic symptoms), and social modelling (i.e., observing other peo-

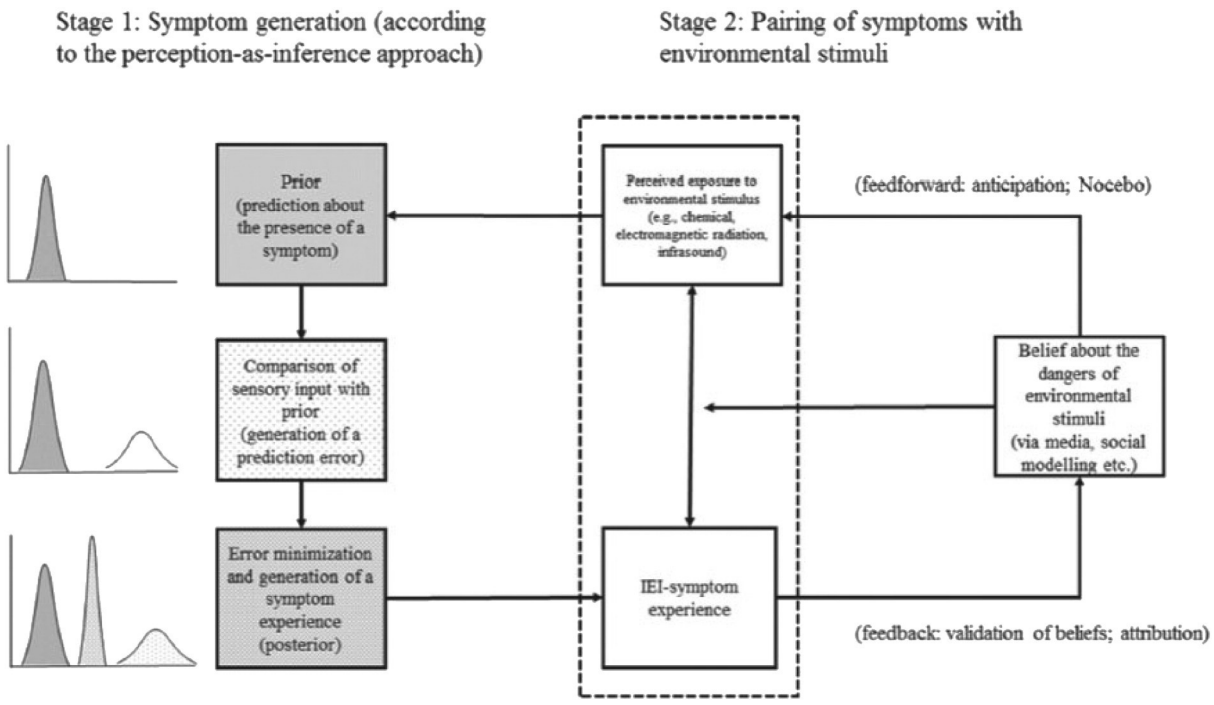

Figure 1. From Van den Bergh, Brown, et al. (2017). Idiopathic Environmental Intolerance: A Comprehensive Model. *Clinical Psychological Science, 5*(3), 551-567, pg. 9

ple reacting in certain ways to environmental stimuli). Once symptom-trigger associations have been formed (stage 2, Figure 1), cognitive (e.g., negative expectations) and behavioral (e.g., avoidance and safety behaviors) processes are hypothesized to maintain and strengthen these symptom-trigger associations, that is: precise prior beliefs or expectations are formed that further bias the symptom perception process. It is worth noting that this symptom generation and maintenance process typically takes place in the absence of conscious insight or control, creating the impression for the patients that the symptoms are indicative of an acute threat to one's physical health. In light of this acute feeling of immediate threat, defensive behaviors (e.g., avoidance of triggers, health care visits, body scans, frequent medical assessments) make perfect sense. Unfortunately, these defensive behaviors that would make sense in the presence of an acute somatic threat serve to maintain strong prior beliefs/expectations, which act as a self-fulfilling prophecy creating more symptoms.

Going back to Tom, his mild allergy to triethylamine (TEA) had obviously instilled a prior belief priming the likelihood of symptom experiences attributed to TEA when he is at work. In retrospect, a number of reasons suggest that the sudden exacerbation that brought him to the emergency unit was a stress-induced hyperventilation episode (HV): There was an excessive workload at that moment due to absence of a coworker while marital problems at home had reduced his sleep quality and had triggered chronic worrying. Also, detailed assessment of the symptom profile at that moment suggested HV-related symptoms (heart pounding, lightheadedness, gastro-intestinal symptoms, tingling sensations, difficulty to breathe), while medical examination did not find physiologic abnormalities. However, this rather spectacular exacerbation of symptoms reinforced his prior belief (made it more precise) that substances in the work environment may trigger symptoms. From here on, nocebo processes alone may take over to elicit symptom episodes. In addition, because the job context has become a source of stress, episodes of (subclinical) HV may occasionally contribute to the symptom episodes and further reinforce highly precise symptom expectancies. Eventually, the anxious (expectancy-based) search for potential symptom triggers outside the job environment may elicit a self-fulfilling prophecy leading to an expansion of the set of triggers able to cause symptoms and to the increase of symptom episodes (generalization). All this results in the clinical picture of Tom being convinced that TEA is the causal factor that has sensitized him to an increasing number of products that are now also causing symptoms almost everywhere, turning his life into a hell. Obviously, his symptoms are real experiences and the fact that medical doctors tell him that his symptoms cannot be explained by TEA makes him hopeless about the future.

Diagnosing IEI and Assessing Symptom Strength

Because many patients report negative experiences with medical consultations (e.g., perceiving that medical personnel are dismissive of their symptoms), a careful diagnostic procedure, both in terms of a medical examination as well as a comprehensive assessment of the symptom and treatment history, may act as a platform for a constructive therapeutic alliance towards an effective treatment of IEI. After an initial clinical hypothesis of IEI, medical differential diagnosis should exclude organic diseases (e.g., neurological diseases following acute and chronic effects of intoxication by environmental chemicals, poly-neuropathy, etc.). However, because the diagnostic process according to the classical biomedical model (e.g., somatic symptoms are indicative of an underlying organ pathology) falls short of accounting for IEI, it is important to provide a clear alternative explanation for the symptoms in the absence of detectable pathology. If only the feedback is given that at a somatic/medical level everything is OK (i.e., no organ pathology detectable), this feedback may enhance the need for explanation (i.e., "If everything is OK, why do I still have these symptoms?") and may drive the patient to consult another medical specialist. This point will be pursued during the psychoeducation part of the following treatment.

Because no objective biomarker or laboratory test exists for IEI, the diagnosis necessarily remains based on self-reports or interview-based clinical evaluations. The use of diagnostic instruments (i.e., specific questionnaires and structured clinical interviews) to assess symptoms and disability signals clinical expertise and conscientiousness. It also allows standardization of the assessment procedure and it can be used to monitor symptomatology over the course of the treatment. Diagnostic instruments should assess and quantify typical IEI-related symptoms and attribution using special questionnaire or interview procedures (Table 1). Also, the broader clinical relevance should be assessed by situating the somatic symptoms and associated features of the patient among the somatic symptom and related disorders category in DSM-5 or the bodily distress disorder category in ICD-11. Additionally, "problems related to the physical environment" (Z58) can be assigned in order to specify the context of IEI. Potential comorbid mental disorders (e.g., depression, anxiety disorders) that frequently co-occur with IEI (Bailer et al., 2005) should be assessed, as well.

The different steps of the diagnostic process are summarized in Table 2. Applying this diagnostic procedure to the patient Tom, outlined above, may result in the following information and diagnostic decisions: Tom is presenting mainly with symptoms characteristic of the IEI subtype related to intolerance to chemicals (step 1). A careful medical examination by a toxicologist, immunologist, or other specialist has found no medical/somatic explanation for his symptoms (step 2). Assessing the symptom strength as well as the exact type and number of triggers (e.g., by using the COSS as well as the IEI interview/questionnaires) shows that Tom reaches a sum score of 42 in the COSS, which is clearly above the suggested cut-off score of 26 for the identification for clinically relevant IEI in men (Bailer et al., 2006). Within the IEI interview (and questionnaires), it becomes obvious that Tom's symptoms are specifically related to a wide range of chemical odors, while no symptoms are attributed to noise or electromagnetic fields. The symptoms are strong and debilitating (i.e., interfering with work-related as well as private life and activities), qualifying for the criterion of clinical relevance of the somatic symptoms. From a purely descriptive perspective, the somatic symptoms presented by Tom could be considered as a "somatic symptom disorder," according to DSM-5 (American Psychiatric Association, 2013). Using a structured clinical interview for mental disorders (e.g., SCID or CIDI) reveals that Tom qualifies for the diagnoses of panic disorder as well as for a major depressive episode (currently mild) (step 3). In a final step, the results of the diagnostic processes should be discussed together with Tom and compared with his personal experience. Although the initial diagnostic process would be terminated at this stage, we recommend a process monitoring of IEI-related symptoms and triggers as well as a systematic outcome evaluation using the same dimensional measures of symptom strength (e.g., the COSS) that have been applied in the initial diagnostic process.

Treatment

The short description of our model (see above; Van den Bergh, Brown, et al., 2017) suggests three main ways of altering the model underlying symptoms as caused by environmental cues, and thereby treating IEI: (a) by altering highly precise prior beliefs so that they account for somatic information in a less disabling way, (b) by providing opportunities for actions to generate information that fits new prior beliefs (active inference), and (c) by influencing the sampling strategy for somatic input (attentional focus). Before elaborating on these goals and on specific interventions to reach them, it appears critical to choose an appropriate treatment setting and to consider prognostic factors.

Table 1
Specific Measures for the Assessment of IEI

Name of the scale	Construct assessed	Cut-off scores for the identification of clinical cases (if available)	Reference
Idiopathic Environmental Intolerance Symptom Inventory (IEISI)	• Variant of IEI (e.g. chemicals, buildings, electromagnetic fields) • Symptoms as a consequence of exposure		(Andersson, Andersson, Bende, Millqvist, & Nordin, 2009) (Andersson et al., 2009)
Environmental hypersensitivity symptom inventory (EHSI)	Various symptoms as a consequence of exposure (e.g. airway, skin and eye, cardiac, head related, gastrointestinal)		(Nordin, Palmquist, Claeson, & Stenberg, 2013)
Quick Environment Exposure and Sensitivity Inventory (QEESI)	IEI attributed to chemicals	Chemical intolerance: 47 Life impact: 21 (Skovbjerg, Berg, Elberling, & Christensen, 2012)	(Miller & Prihoda, 1999)
Chemical Odor Sensitivity Scale (COSS)	IEI attributed to chemicals	Women: 30 Men: 26	(Bailer, Witthöft, & Rist, 2006)
Modern Health Worry Scale (MHWS)	Concerns and worries about the harmfulness of everyday low-level exposure concerning electromagnetic fields, chemicals, genetically modified food, etc.		(Petrie et al., 2001)
Idiopathic Environmental Intolerance Inventory (IEII)	• Variant of IEI (e.g. chemicals, buildings, electromagnetic fields) • Symptoms as a consequence of exposure • Impairment in central aspects of daily life (e.g. family, work, social life)		(Supplement)

Table 2
Suggested Steps of the Diagnostic Process in Persons at Risk for IEI

Step	Procedure
1	General anamnesis (assessment of symptoms and case history)
2	Medical examination to rule out (somatic, neurological, and psychiatric) processes as sources of the symptoms. Allergologic and toxicologic investigations of the patient's environment may be considered if indications of their relevance are present.
3	Careful assessment of symptoms and disability using specific questionnaires (Table 1) and structured clinical interviews for IEI and potential co-occurring mental disorders
4	Feedback of diagnostic results (at the beginning of therapy)
5	Process diagnostic over the cause of the treatment (i.e. monitoring of symptom strength in order to detect symptom improvements as well as deteriorations)
6	Outcome evaluation (assessment of symptoms at the end of treatment and comparison to symptom-levels at the beginning of treatment)

Treatment Setting

The treatment program outlined in the following sections is originally designed for an outpatient setting with 1–2 weekly individual therapeutic sessions with a duration of 50 min each. According to our experience, treatment duration varies largely, with some cases responding within 6–8 sessions and others that need more than 15 sessions. Depending on the severity of the current symptom distress as well as on the degree of avoidance behavior (for example, when the symptoms prohibit the patient to travel to the ambulatory treatment setting), inpatient treatment (with specialized exposure-free facilities) might be necessary. In case of very severe, chronic and generalized symptoms, involving significant avoidance behavior of potential triggers (e.g., smells or radiation), multidisciplinary inpatient treatment settings consisting of medical specialists (e.g., toxicologists, immunologists, allergists, neurologists, psychiatrists, occupational medical specialists), as well as psychotherapists, are recommended. It is noteworthy, however, that such treatment settings are generally rather rare and available only in certain countries (e.g., the Netherlands). Inpatient treatments, if available, should be of limited duration (e.g., 2–4 weeks, to prevent negative aspects of hospitalization such as generalization of avoidance behavior) with a focus on diagnosis and differential diagnoses. This inpatient phase should be followed by a more extensive outpatient treatment phase. Also, certain treatment approaches and settings might also be incompatible: in this regard, a cognitive-behavioral or behavioral medicine approach (as outlined in this article) focusing on self-efficacy and regaining tolerance towards potential triggers appears rather incompatible with a purely biomedical approach that relies on strictly avoiding suspected IEI triggers and detoxification procedures based on assumed hypersensitivity towards chemicals. Related to this issue, out of desperation, many patients (and doctors) adopt a "the more the merrier" treatment strategy, leading to accumulating treatments of different kinds, which we consider counterproductive. It therefore appears reasonable to carefully inquire about alternative treatments during the diagnostic stage. If necessary, incompatible treatment options can be put in a sequential order or the outlined treatment program could be postponed until the alternative treatment has ended.

Prognostic Factors for a Complicated Treatment Course

Based on our clinical experience, we consider the following factors as indicative of a more complicated and less successful treatment course and outcome: current unemployment (e.g., due to sick leave, loss of job, or early retirement), claims for compensation (e.g., due to inability to work), longer illness duration (> 2 years), multiple and costly actions that have been taken to avoid or remove IEI triggers (e.g., reconstruction works, consultation of self-declared specialists in the realm of alternative medicine), higher number of prior treatments and/or of medical specialists so far consulted. Furthermore, an active role in IEI activist groups striving for societal measures to reduce exposures as well as the lack of a supportive social network (friends, family) and other personal resources (e.g., hobbies) constitute further complicating factors. These factors do not necessarily represent a contraindication for the outlined treatment program but should be carefully considered when setting treatment goals and planning the overall treatment duration. In case of many coexisting negative prognostic factors, a provisional therapy phase (on a trial basis) might also be helpful to evaluate together with the patient whether the offered treatment rationale is acceptable and promising enough to start the full program. In this regard, high levels of ambivalence and skepticism towards psychotherapy are frequently observable in patients with IEI and can also be addressed in a first provisional therapy phase (see the next section).

Psychoeducation

Because patients suffering from IEI typically rely on a rather strict somatic-physical disease model, they are often ambivalent and skeptical about a psychological approach of their problem. To address this skepticism, it appears helpful to explain that psychotherapists do not exclusively work with patients suffering from mental disorders but also with patients primarily impaired by physical diseases like diabetes, high blood pressure, asthma, and cancer. As a second step, patients who are unfamiliar with psychotherapy so far should be briefly informed about the characteristics of the psychotherapeutic setting (as compared to a traditional medical setting). Such characteristics involve a cooperative relationship intending to promote self-help and self-efficacy, with clients becoming gradually experts for their problems, and the idea that activities (e.g., behavioral experiments) between therapeutic sessions ("homework") are an important treatment component. As a next step, treatment expectations should be collected and goals should be discussed in cooperation with the patient, with a focus on *realistic* goals (e.g., a decrease of symptoms and a substantial increase in quality of life along the process with—very likely—several ups and downs in contrast to an immediate "healing"). Treatment goals might also be structured along the time scale (short vs. long-term goals) and should always be put down in writing to allow for an outcome evaluation later in therapy.

Once basic information concerning the treatment setting has been provided, the first important step is to provide a clear and convincing explanation to the patient for his/her physical symptoms in response to the environmental cues, and to explain the different phases in the treatment as a logical consequence of how the symptoms come about. If successful, a shared illness theory may emerge that serves as a basis for a productive therapeutic alliance and will foster the patient's engagement for the treatment. If not, the patient most likely will stop here. Two reasons make this step extra critical: first, most patients will have consulted several medical experts in the past, with often conflicting explanations and generally poor hopes for help, so the question arises why it would be different this time; second, psychological treatment is often a priori considered inappropriate for physical symptoms and a denial of the wish to be taken seriously (that is, having "true/real" symptoms). Therefore, following the diagnostic process, it is of ultimate importance to take sufficient time for this psychoeducational step. If possible, consider inviting the partner: an extra supporter of the treatment process is better than an extra sceptic. Also, the style and phrasing of the psychoeducational messages needs to be adapted to the particular case and educational level of the patient but should contain the following main elements.

1. *Linking Up With the Patient's Anamnestic Information*

This step is important to understand (and explain) how the patient became sensitive to the potential harmful role of environmental cues. Usually the following elements play a part in the patient's history: a toxic exposure in the past, a particularly negative experience such as a sudden bout of symptoms, observing a dramatic story of how another person got sick in response to a particular environmental trigger. The patient's story will typically demonstrate that an aversive symptom episode happened that was either perceived as a direct response to an environmental cue and/or that the patient in retrospect came up with a causal explanation attributed to salient environmental cues (e.g., a pungent odor). In both cases, the critical part of the story is that the patient has established a predictive relationship (highly precise prior belief) that causally links symptoms to environmental triggers, implying the anticipation of a new aversive symptom episode whenever the trigger is encountered. Referring to our example: linking up with Tom's anamnestic information (i.e., the sudden exacerbation of symptoms that brought Tom to the emergency unit) is important to establish a trustful therapeutic relationship. It ensures that the therapist is aware and understood the critical events in the course of the illness development process.

2. *Explanation of the Stress Response System and How It Can Produce Somatic Symptoms*

Stress-related hyperventilation (HV) is often involved in IEI cases (Leznoff, 1997). If the symptom pattern is consistent with it, it can be explained how a combination of stressors and/or repetitive negative thinking (worry, rumination) can elicit a variety of symptoms through a subtle increase of minute ventilation in excess of the metabolic needs. HV is a highly prevalent stress response with symptoms that are variable and hard to objectify and—therefore—often highly distressing. HV can play a critical part at the start of the process (see 1 above) and/or it can become involved as a perpetuating process. However, also other stress response systems can be involved, conjointly or separately with the respiratory system, such as the autonomic system and possibly the endocrine-immune system. The bottom-line here is that, once aversive somatic experiences are anticipated, the stress response may become triggered by the anticipation of symptoms alone, thereby inducing somatic responses that may underlie symptoms.

3. *Explaining Nocebo Effects*

An important further complication is that once clear cue-based expectations have been established, the anticipation itself can cause the experience of symptoms. This has been shown in several conditioning experiments (see Van den Bergh, Brown, et al., 2017, Table 1, for an overview): after a number of experiences of a symptom episode associated with harmless odor cues, the latter cue alone can elicit symptoms by itself. In other words, nocebo effects emerge. However, expectations can also develop following verbal information (e.g., nocebo suggestions) and social observation (Vögtle et al., 2013). Because the idea that symptoms can emerge without physiological dysfunction is rather new and often hard to believe for the patient, strong metaphors may be used to convince the patient of the importance of this mechanism. Two types of metaphors are particularly instructive. In the first type, real somatic responses are elicited by mental processes. For example, in the "lemon and saliva" story, simply vividly thinking/imagining a scene in which one is sensing the taste of lemon juice is sufficient to induce measurable bodily changes (increase in saliva production). Another metaphor is the "near car accident and heart pounding" story (see box). The other type illustrates that somatic responses may not even be necessary to induce a particular somatic experience, such as the "drowning and breathlessness" story (see box).

1Such examples, especially when the patient is invited to experience the somatic effects, are usually quite convincing. The message to the patient here is that the brain makes a model (or representation) of

repeated symptom episodes and that contexts or cues by which the model is reliably and strongly activated may recruit the brain structures representing the model, thereby causing actual symptom experiences (either or not accompanied with actual changes in the bodily responses). It is good to emphasize that activation of the mental model typically happens automatically and often unconsciously (much in the same way as shifting gears represents a way of "thinking" of the brain which goes unnoticed and automatically; Bräscher et al., 2018). As a consequence, changing this process may be the most difficult step and may take some time. It may be helpful here to expand on how the brain works, and on how previous experiences and expectations impact on our conscious experience. A homework assignment may involve watching a number of examples on YouTube (rubber hand illusion: https://www.youtube.com/watch?v=sxwn1w7MJvk; Checkerboard illusion: https://www.youtube.com/watch?v=QirAG58U1FY).

The elements 2 and 3 are intended to challenge highly precise prior beliefs and to suggest a new model to think about the symptoms in a less disabling way. This means in our example that Tom's model of how his symptoms come about—and thus his implicit predictions about what will happen with new confrontations with triggers—is challenged and that he is invited to consider and test an alternative model. We believe, however, that the neural processes in the brain that are governing the symptom experiences are not simply altered by providing verbal information and that behavioral experiences will have more fundamental impact on (implicit) perceptual inference and predictions.

Box

The lemon effect

"*Please close your eyes and try to vividly imagine that I hold a lemon in front of you right under your nose. You can smell the odor of the lemon. Imagine that I cut it in two parts and that I hold one part right under your nose: you can now very clearly smell the lemon odor. Now, imagine that you take a bite: you put your teeth into the lemon flesh and suck up the sour juice that starts to flow into your mouth. The acidity triggers your saliva glands. After a while you feel your mouth full of saliva. . .*"

Most persons will quickly report that they feel an increase of saliva in their mouth. The patient can be told that this is an illustration of a very important mechanism: activating a model in the mind of previous experiences with lemons may result in real physical responses to mental events: the saliva is real, the lemon is not. People who never had the experience of tasting a lemon would probably not or very little feel the saliva flowing.

The near-car accident

"*Probably you ever have had a near car accident. About half a minute later, your heart starts to pound really hard, sometimes for several minutes. When you go to bed several hours later and your mind starts wandering, all of a sudden the image of the near car accident may pop up into your mind. As if it were real, your heart starts to pound again. Nevertheless, you lie safely in your bed.*"

This example again illustrates the mechanism that mental models in the brain can trigger real somatic symptoms.

The breathlessness episode

"*I once saw a movie about hikers in the huge forests of Northern America. At some point, they wanted to cross a river. In order to do so, they cut a tree such that it fell over the river, allowing them to cross it. However, something went wrong during this operation and one of the hikers got stuck under the tree and was pushed under water by the heavy weight of the tree. Spectators of the movie could see a person drowning very slowly, almost centimeter by centimeter. One could see the actor in the movie desperately gasping for air. When I watched the audience for a moment instead of the movie, I could see almost 80% of the spectators increasing their ventilation, and many even gasped for air or took deep breaths. Apparently, they felt slightly breathless themselves.*

This example is in some ways different: there is no obvious physiological response that caused breathlessness (as was the case in the lemon and car accident example). Just the vivid imagination of breathlessness — that is: activating a mental model about it caused the sensation, which subsequently changes breathing. Interestingly, an increase in breathing driving ventilation in excess of the metabolic needs induces hyperventilation which actually induces breathlessness and several other bodily symptoms.This example shows that a mental model can induce the sensation of a symptom that subsequently changes physiology in such a way that more symptoms are elicited.

4. *Eliciting Symptoms by Environmental Cues*If the patient is willing to accept being exposed to a critical trigger, it is always instructive to include it because behavior during confrontation can be observed and psychophysiological responses can be measured. For example, several patients with MCS start respiratory maneuvers in response to odor cues (sniffing, coughing, spitting and swallowing, gasping and rapid breathing, etc.). Measuring $PetCO_2$ during the exposure episode helps track whether HV is involved in the response to the odors. Also, other surface mea-

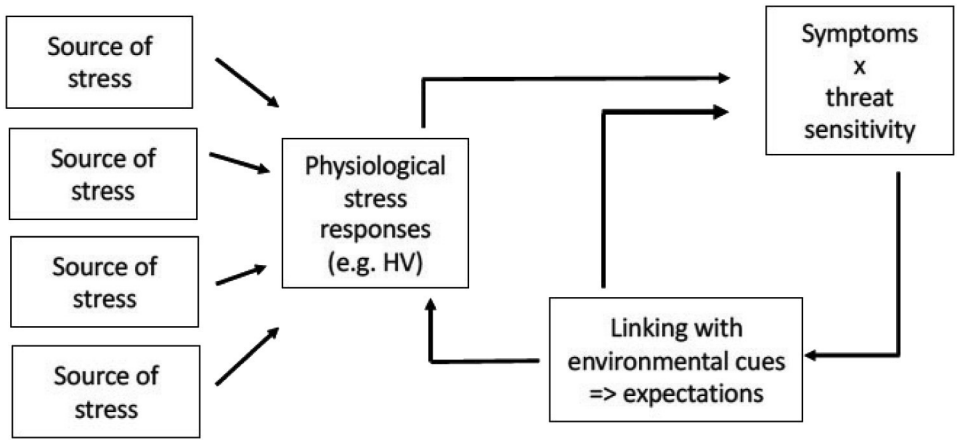

Figure 2. A simple model describing two vicious circles that are suggested to operate in IEI patients. It can be helpful to use it in a psychoeducational phase for patients (HV: hyperventilation).

sures of the stress response systems can be taken (heart rate, skin conductance, muscle tension, etc.) to inform about stress reactions in response to the cues. Eliciting the symptoms by environmental cues is a way to provide action-based experiences that generate information to suggest and reinforce new prior beliefs (active inference).The different steps above will typically result in a set of elements that allow depicting a model that explains the patient's condition (see Figure 2). In addition, it also allows to indicate in the schema which therapeutic steps should be taken. These steps are as follows:

1. Coaching the patient how to manage the stress response to environmental cues (e.g., HV if this is involved, or learning to reduce a general arousal state state through relaxation).
2. Coaching the patient to drop vivid anticipations of symptoms and to inhibit a defensive response activation in response to cues (e.g., sniffing, swallowing, gasping and rapid breathing, increasing muscle tension, or other types of avoidance and controlling behavior) by adopting a "let go" attitude during exposure.
3. Exposing the patient to the environmental cues, while performing Steps 1 and 2. This may involve making a hierarchy of the triggers according to the level of distress they cause.
4. Coaching the patient to reduce avoidance behavior, including checking and controlling one's own bodily responses, continuously going on the internet to read about the multiple ways one's symptoms may come about, etc.
5. Often the problems emerged in the context of wider stress problems and/or are comorbid with other mental problems (anxiety, depression, somatization, health anxiety, etc.). These problems can be tackled along the way and more to the end of the treatment.

Steps 1 to 4 are intended to generate action-based information (active inference) that suggest and reinforces an alternative causal model for the emergence of symptoms. Obviously, the experience that symptoms in response to triggers have a reduced intensity or remain absent, while similar symptoms can be produced in the absence of the triggers, will undermine the highly precise prior beliefs of the "pathological" causal belief system and gradually help to install new prior beliefs (see further). Learning how to manage stress and giving up defensive response activation associated with anticipating new symptom episodes is also intended to alter the sensory sampling strategy for somatic input. Since attention is assumed to act as a gain factor on neural processing of incoming information (by increasing the precision of the sensory information), less (precise) somatic input will be available for perceptual inference leading to the experience of symptoms.This psychoeducational phase may take up to 2 hours and is characterized by an active working atmosphere and an empirical (i.e., open, curious, and nonjudgmental) attitude towards the symptoms, in which the therapist joins the patient as a coach trying to get a grasp of the symptoms and their causes (the "detective/Sherlock Holmes metaphor"). Further guidelines are as follows: (a) to empathize with a critical attitude towards the presented account of the symptoms because, at first sight, it is at odds with the personal experience of the patient as well as with a traditional biomedical perspective on symptoms and the body; (b) to avoid starting a discussion on the "true source" of the symptoms, and to motivate the patient to give the perspective a chance and some time to experience the effects of the approach; (c) to emphasize that symptoms are as real as any other symptom: mental processes can recruit roughly the same brain structures associated with the conscious experience of symptoms as the ones that are activated by input from peripheral somatic dysfunction.

Cognitive–Behavioral Intervention Steps

1. *Managing the Stress Response*

Coping with respiratory stress responses, especially when respiratory maneuvers are carried out inducing hypocapnia (i.e., a state of reduced carbon dioxide in the blood, usually resulting from hyperventilation), implies learning how to apply closed circuit breathing (expired CO_2 is inspired again) and/or pursed lip breathing (slowing down expiration of CO_2). This involves hyperventilation provocation to induce symptoms in the first place. Often it is an eye opener for a patient to experience symptoms after just a short period of enhanced breathing through increasing frequency and/or volume. These symptoms will likely to some extent overlap with symptoms in response to environmental cues, and in that case provide an excellent challenge of the perceived causal link with the cues. Brief relaxation training focusing on developing a "let go" attitude rather than on muscle relaxation may further complement this or can be the focus of this step if there is no evidence for HV. The general message here is to coach the patient to reduce and eventually eliminate the tendency to mobilize the defensive response system when encountering the supposedly threatening environmental cues. In the case of Tom, it was important for him to experience that similar symptoms as experienced in response to triggers could be elicited by HV provocation in the absence of those triggers, thereby invalidating his "maladaptive" generative model of symptoms.

2. *Exposure to the Environmental Cues*

Listing the environmental cues in a hierarchical order representing their level of threat/symptoms. Each hierarchical level is a step in this exposure phase of the treatment (although strictly following the order is not necessary; Craske et al., 2014). If the therapist has no access to such cues (particular chemicals, odors, etc.), patients are asked to bring them along. Alternatively, treatment takes place in the natural environment where the cues are present. The goal is to systematically expose the patient to the cues while keeping the stress response as low as possible by activating the "let go" attitude to counteract the mobilization of the defensive response system. It is important to motivate the patient to practice each hierarchical step at home to consolidate every step forward before moving to the next one.

In the case of Tom, exposure to a hierarchical set of triggers (e.g., cleaning products, fresh paint, smoke, perfumes, deodorants, washing products, soap, etc.) allowed him to experience that they did not necessarily elicit symptoms with the same intensity, or not at all, if he remained relaxed. Importantly, many cases are "mixed" like Tom: a mild allergy to some substances may be involved, but the clinical picture is almost entirely determined by IEI-related processes. Exposure to the allergic triggers may be explored to show that the response to it has diminished to its physiologically determined level. However, this step is only advised if the patient explicitly wishes to explore it and has been medically guided to handle the symptoms. It is not considered a necessary therapeutic step in the context of IEI: behavioral avoidance of true allergic triggers is a healthy strategy.

3. *Linking Up With the Nocebo Explanation (see section on psychoeducation)*

It may be reemphasized that symptoms may come about through automatically and unconsciously activating the mental model underlying the experience of symptoms by cues and expectations. This means that symptoms may also emerge regardless of the activation state of the stress response system. However, this is more likely when attention is chronically focused on the cues to early detect or predict symptoms. The message here is that chronic concerns and tendencies to fight the symptoms are understandable, but that they are actually counterproductive ("just like trying to grasp sand: the harder the force to grab it, the less you keep"). The implication is that the patient should be coached to accept the occasional presence of the symptoms for some time ("giving up fighting the symptoms") while focusing on normal, if possible, pleasant activities that are able to catch and keep the patient's attention going (cf. above: altering the sampling strategy of information).

4. *Interoceptive Exposure to and Acceptance of the Bodily Symptoms*

An attitude of acceptance towards somatic symptoms is typically difficult to develop because it is squarely opposite to the attitude that the patient has maintained and "trained" during a long time. At first, we suggest that therapists and patients together collect as many potential explanations for the respective symptoms as possible, without prematurely dismissing patients' first causal explanations. This "pluralism of explanations" automatically lowers the patient's strong focus on the first (environmental) causal explanation and allows for the consideration of alternative explanations. This first step might be followed by a careful consideration of available evidence in favor and against every single causal factor and should eventually lead to—at least—allowing doubts about the cause of the symptoms ("It may not be an allergy") and/or adopt a wait-and-see strategy towards the symptoms ("We will see what happens after some time"). The attitude of acceptance includes an element of interoceptive exposure to normal and harmless

somatic sensations (e.g., some slight headache, concentration problems, racing heartbeat, sweating, breathlessness). This attitude can also be trained and fostered by actively provoking harmless somatic symptoms by using interoceptive exposure techniques. Actively and deliberately provoking somatic symptoms (e.g., climbing stairs, doing squats, voluntary hyperventilation, spinning on an office chair in order to provoke dizziness) also creates a feeling of control over these symptoms in patients because they realize that they are able not only to tolerate symptoms but also that they are able to "create" symptoms. Implicitly, these experiences should be able to lower the threat value of somatic symptoms in patients.

5. *Behavioral Exercises to Gradually Reduce Avoidance Behavior and Reinstall Normal Activities*

Because avoidance behavior is critically involved in the preservation of problematic IEI-related priors, overcoming avoidance represents one of the most powerful treatment elements. Healthy behavioral activity might be (re-)established by using daily or weekly protocols. The degree and type of activity should thereby be tailored to patients' individual physical fitness levels. Behavioral exercises together with therapists can also be planned as part of the therapeutic session if exposure to critical environmental triggers runs the risk of reactivating avoidance and/or becoming overwhelmed by stress. Another important strategy is to promote (resuming of) activities that are instrumental to reach the patient's life goals and positively contribute to his/her well-being. This typically involves restoring and developing professional skills, returning to work, taking up hobbies, and resuming and social contacts.

In the case of Tom, Step 3, 4, and 5 suggested a new model about the causal mechanisms underlying his symptoms, which he was invited to further test and challenge in an open, explorative way through repeated exposure to symptoms and triggers.

6. *Ameliorating the Broader Context of Life*

Our work with patients suffering from IEI suggests that contextual factors are often importantly involved in the maintenance of this condition. Such contextual factors that serve as potential stressors involve problematic family constellations (financial problems, conflicts with partners, chronic illness, etc.), occupational problems, as well as loneliness in some cases (of older patients, for instance, after retirement). Because stress and associated negative affect fuels somatic symptoms and thereby the formation of IEI symptoms, it appears essential that therapists consider these contextual factors and coach patients to develop and implement problem-solving strategies and skills. Comorbid mental disorders (e.g., depression and anxiety) should also be addressed at this stage by using evidence-based treatments protocols. It is noteworthy, however, that many aspects mentioned as part of this treatment manual also represent standard treatment elements when it comes to depressive and anxiety disorders (e.g., cognitive restructuring, behavioral activation, enhancement of positive activities, and exposure to avoided cues in terms of anxiety). In Tom's case, his occasional work overload and his marital problems were elaborated on in a standard CBT approach.

Monitoring Treatment Progress

0Process evaluation of treatment progress should be implemented routinely (about every second to third week, e.g., by using dimensional measures of IEI symptom strength and disability as presented in Table 1; dimensional measures of general distress, quality of life, and comorbid psychopathology can be used in addition). Results of the process evaluation should always be reported back to and discussed with the patient. The continuous evaluation of treatment progress allows for an early detection of nonresponse and deterioration effects that would necessitate a change of treatment focus and strategy. In addition to this standardized assessment of symptom strength and distress, therapists are encouraged to routinely request feedback from their patients at the end of each session (using open-ended questions: What was most important for you in our session today? Which new experiences did you make? What should be the focus of our next session?). Such questions help to foster and consolidate new learning experiences and represent opportunities for the correction of potential misunderstandings that may have arisen throughout the therapy session.

Treatment Termination and Relapse Prevention

Treatment can best be tapered off by gradually reducing the frequency of appointments and by putting more weight on the patient's homework between sessions. Discussion of the homework experiences and results may gradually evolve into a discussion of the treatment results in general and of the process that has led to it. This may further provide insight into the critical mechanisms and reinforce the strategies that have been used to get to the treatment result. These discussions convey important messages to the patient:

- It remains important to continue the different types of exercise, such as stress management, exposure to triggers and symptoms, problem solving and the development of strategies to improve well-being in general. The idea is that continued exercise will

help to automatize thoughts and behaviors, meaning that they cease to feel as exercises requiring effort after some time.

- The patient should be made aware that moments of relapse are always possible. Typically, relapses occur in response to cues that are not frequently encountered in real life (i.e., many exercises have been directed to handle a particular trigger). A relapse in response to one trigger may partly generalize to other triggers and symptoms. The message to the patient here is that progress is never entirely lost and may be regained rather quickly using the same strategies. In addition, by addressing risk situations for relapse reinforces the treatment progress on the longer term.
- It might be good to follow up with the patient for a long time, but at low frequency. This strategy may contribute to the motivation of the patient to continue working on his/her problem ("in x months, the therapist will be asking questions about it"). In addition, the patient may feel assured that the therapist remains available for relapse or difficult moments to help overcome potential setbacks.

Conclusion

We described a systematic treatment approach for IEI-related health problems, based on a novel explanatory model to understand IEI on the one hand and on principles of cognitive-behavioral therapy to change these problems on the other hand. The goal is to facilitate systematic research, possibly RCTs, to treat these patients.

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