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The effect of anxiety sensitivity and expectancy manipulation on panic-like response to the 35% CO_2 challenge

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To my sister

Abstract

The Anxiety Sensitivity (AS) theory, developed by Reiss and McNally, refers to the fear of anxiety-related bodily sensation, due to the belief that they are psychologically, physiologically, and socially harmful. In this field several researches established the relationship between AS and panic: subjects with High AS (HAS), compared to Low AS (LAS), had greater panic-like responses when the carbon-dioxide (CO_2) challenge was administered. Telch and colleagues suggested that the standardized instructions for the CO_2 challenge might influence the anxiety response to the test in healthy subjects. Surprisingly, they found that HAS subjects (*versus* LAS), randomized to Expected Relaxation instructions (ER) (*versus* standard Expected Arousal instructions - EA) had higher panic response to the 35% CO_2 challenge compared to room air inhalation. Thus, the aim of the present research was to replicate Telch and colleagues' study in order to overcome some methodological limitations and verify if AS, and the manipulation of expectations, might affect the psychological and physiological responses to the 35% CO_2 challenge.

Sixty-eight healthy subjects, matched for sex, age, and opposite level of AS (HAS *versus* LAS), as measure by the Anxiety Sensitivity Index - 3 (ASI-3), were randomized to one of two instructional set (ER *versus* EA). Immediately before and after the 35% CO_2 challenge and room air inhalation, they filled the Visual Analogue Scale of Anxiety (VAAS), of Fear (VAS-F), of Discomfort (VAS-D), and the Panic Symptom List (PSL). Physiological parameters (i.e., systolic and diastolic blood pressure, heart rate) were also measured. Hierarchical multiple regression showed greater psychological responses at VAAS, VAS-F, VAS-D, and PSL, and higher systolic blood pressure under CO_2 compared to room air. The psychological and physiological response to the test was not affected by the level of AS (HAS *versus* LAS) or the instructional set (Expected Arousal *versus* Expected Relaxation).

The present study confirmed the psychological effect of CO_2 challenge on emotional responses of healthy subjects and strengthens the goodness of the standardized instructions used to administer it.

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Chapter 1. Introduction

1. Anxiety

The core characteristic of human being is the awareness and understanding of emotions. Their innate and adaptive nature consent human development and personality functioning (Izard, 1972). Pioneering in this field was the research of Paul Ekman, who described for the first time the six basic and universal human emotions: anger, disgust, fear, happiness, sadness, and surprise (Ekman & Friesen, 1971). From a psychological perspective, emotions have been extensively studied both examining their adaptive nature, but also in generating suffering or psychopathology.

Focusing on emotions of fear and, the related, anxiety, many authors proposed different conceptions.

According to the neo-evolutionary approach, fear is a basic emotion present across ages, cultures, and species. It is universal, innate, and has a specific adaptive value (Barlow, 2002; Willers, Vulink, Denys, & Stein, 2013). Usually, fear is defined as an alarm response to present or imminent danger (Craske, Rauch, Ursano, Prenoveau, Pine, & Zinbarg, 2009). Anxiety is a future-oriented mood state, characterized by apprehension due to the ability, or unpredictability, to control upcoming events (Barlow, 2002). According the Diagnostic and Statistical Manual of Mental Disorder - Fifth edition (DSM-5; American Psychiatric Association [APA], 2013) “fear is the emotional response to real or perceived imminent threat, whereas anxiety is anticipation of future threat” (p. 189).

Fear is characterized by a massive response from the autonomic nervous systems, necessary for flight or fight behaviour; anxiety is often associated with vigilance and muscle tension, in preparation for future danger. It involves three-response system (Craske et al., 2009): verbal-subjective symptoms (i.e, worry), overt motor acts (i.e., avoidance), and somato-visceral activity (i.e., muscle tension).

An interesting distinction between fear and anxiety was proposed by Robert and Caroline Blanchard in 1988 (Blanchard & Blanchard, 1988). They linked a set of behaviours that normally occur when we are exposed to a threatening stimuli or a predator. The set of behaviours includes, risk assessment, elicited by potential, abstract or signalled threat (Blanchard, Blanchard, Griebel, & Nutt, 2008). Thus, according to the Blanchard, the difference between fear and anxiety is related to the proximity *versus* ambiguity of the threat. Debating this theory, McNaughton and Corr (2004) proposed fear as the active avoidance of a threatening condition (i.e., leaving a dangerous situation); conversely, anxiety corresponds to approach behaviour (i.e., entering in a dangerous situation) or passive avoidance (i.e., refusing entrance in a dangerous situation). As stated above, anxiety is an adaptive response characterized in its normal manifestation by limited intensity and duration. In fact, according to the Yerkes-Dodson law (Yerkes & Dodson, 1908) in which a task outcome relates to arousal in an inverted U-shaped function, the performance or the adaptive responses to the environment increase when the level of anxiety is moderate. On the contrary, very high or low level of anxiety decrease the performance or the probability to elicit adaptive responses drastically (Yerkes & Dodson, 1908). However, when the anxiety responses are out of context, exaggerated, inappropriately timed, and/or irrational, they cause dysfunction and trigger self-defeating defensive responses (i.e., symptoms) (Phan, 2015). Therefore, the anxiety threshold is too low and the rate of false alarms is overly high: this is pathological anxiety (Barlow, 2002; Willers et al., 2013).

1.1. Anxiety disorders

The DSM-5 (APA, 2013) has classified anxiety disorders according to the typical age at onset, the types of objects or situation able to induce fear, anxiety or avoidance responses, and the associated cognitive ideation.

Compared to the Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition, Text Revised (DSM-IV-TR; APA, 2000), the DSM-5 has changed. Obsessive-Compulsive Disorder

(OCD), Post-Traumatic Stress Disorder (PTSD), and Acute Stress Disorder were moved to the "Obsessive-compulsive and related disorders" chapter, and to the "Trauma- and stressor-related disorders" chapter, respectively. Conversely, Separation Anxiety Disorder and Selective Mutism, historically included in "Disorders Usually First Diagnosed in Infancy, Childhood, or Adolescence" of DSM-IV-TR (APA, 2000), were moved to the "Anxiety Disorders" chapter (http://www.dsm5.org/documents/changes%20from%20dsm-iv-tr%20to%20dsm-5.pdf).

The DSM-5 identifies the following as anxiety disorders: Separation Anxiety Disorders; Selective Mutism; Specific Phobia (SP); Social Anxiety Disorder (or Social Phobia) (SAD); Panic Disorder (PD); Panic Attack (specifier) (PA); Agoraphobia; Generalized Anxiety Disorder (GAD); Substance/Medication-induced Anxiety Disorder; Anxiety Disorder due to another medical condition; Other specified Anxiety Disorders; Unspecified Anxiety Disorders.

1.2. Epidemiology of anxiety disorders

Anxiety disorders are the most prevalent group of psychiatric disorders (more than twice as frequent as mood disorders) and are associated with high health care cost and burden of disease (Emmelkamp & Ehring, 2014; Bandelow & Michaelis, 2015). Data from epidemiological studies have shown that approximately one third of the population is affected by anxiety disorders during their lifetime. Concerning European countries, Wittchen and Jacobi (2005) reported that the 12-month prevalence rates of anxiety disorders were around the 12%. The Epidemiologic Catchment Area Program (ECA; Regier, Narrow, Rae, Manderscheid, Locke, & Goodwin, 1993), the National Comorbidity Survey–Replication (NCS-R; Kessler, Chiu, Demler, Merikangas, & Walters, 2005$_a$), and the European Study of the Epidemiology of Mental Disorders (ESEMeD; Alonso, & Lepine, 2007) pointed out that the most frequent anxiety disorders were SP and SAD (Bandelow & Michaelis, 2015). Data from an Italian sample (De Girolamo et al., 2006), within the ESEMeD, showed a lifetime prevalence of 10.3% for any anxiety disorders; concerning the past 12-months the

prevalence rates were about 5%. Similarly to other countries, the most common anxiety disorders in Italian population were SP (lifetime prevalence 5.7%; 12-month prevalence 2.7%) and SAD (lifetime prevalence 2.1%; 12-month prevalence 1%).

Concerning sex differences a numbers of studies have reported a higher prevalence in women; specifically, the 12-month prevalence in females is approximately twice higher for PD, GAD, SAD, and SP, and three times higher for agoraphobia compared to males (Bandelow & Michaelis, 2015). Same results were observed in the Italian sample (De Girolamo et al., 2006). Authors suggested that the higher prevalence in women could be due to some psychosocial (such as chronic stressors or childhood sexual abuse), genetic, and neurobiological factors. Indeed, puberty, pregnancy, and menopause are important precipitants for onset, exacerbation, recurrence, and relapse of anxiety and related disorders (Stein & Vythilingum, 2015).

The median age of onset of anxiety disorders is 11 years (Kessler, Berglund, Demler, Jin, Merikangas, & Walters, 2005$_b$). The most common disorders in the range 7 to 17 years are: SP, SAD, separation anxiety disorder, and agoraphobia. Panic disorder and GAD have a later modal age of onset, typically in the early-mid twenties. The prevalence rate of anxiety disorders decrees in the 50 - 64-year group (Bandelow & Michaelis, 2015; Kessler, et al., 2005$_b$).

The early onset of anxiety disorders is commonly paired with the sequential development of another psychiatric condition; actually, comorbidity with psychiatric disorder, even with anxiety disorders itself, is very common. For example, it was found that women with an anxiety disorder had a higher risk to develop bulimia nervosa, major depressive disorder, or another anxiety disorder comparing to men. Conversely, men with an anxiety disorder were found to be more likely than women to be diagnosed with substance use disorders (except drug dependence, in which no differences for gender were observed) (McLean, Asnaani, Litz, & Hofmann, 2011). Adolescents with anxiety disorders also showed an increased risk for suicide attempts (Sareen, et al., 2005).

Costs associated with anxiety disorders are high and involve reduced educational attainment, marital instability, low occupational, and financial status. Thus, prevention programs and timely treatments are important to reduce adverse outcome, but also to reduce the staggering societal cost of anxiety disorders (Bandelow & Michaelis, 2015).

1.3. Aetiology of anxiety disorders

A growing body of research have shown that a complex interaction between neurobiological, psychological, social, and environmental factors could explain the aetiology of anxiety disorders (Barlow, 2002; Emmelkamp & Ehring, 2014).

Data from twin studies, and also secondary cases in families of probands affected with anxiety disorders, suggested a familial and a moderate genetic component for this class of disorders (Maron & Shlik, 2014). According to a meta-analysis on genetic epidemiology of anxiety disorders (Hettema, Neale, & Kendler, 2001), the estimated heritability ranged from 30% to 40%; the only exception was for phobia in which the estimated heritability vary from 50% to 60%. In general, the genetic risk for anxiety disorders has been found significantly lower compared to other mental disorders such as schizophrenia and bipolar disorder.

Concerning anxiety pathogenesis, the most studied candidate genes were those related to serotonin (5-HT), dopamine, cholecystokinin, or adenosine systems. Recently, studies on candidate genes related to hormonal, opioid, immune, neurotrophic, and other systems have being carried out, with increasing evidence showing the involvement of corticotropin-releasing hormone receptor 1 (CRHR1) in anxiety regulation (Maron & Shlik, 2014; Müller et al., 2003). Few studies have examines the gene-environment interaction (G x E) of anxiety disorders. G x E studies imply that the development of a specific disorder could be due to the relation between genes and environmental factors (Gross & Hen, 2004). Abuse and loss/separation experiences in childhood, or recent stressful life events, have been identified as crucial in the development of anxiety disorders

(Klauke et al., 2011). In particular, anxiety sensitivity (AS; for details see paragraph 3) has been found to be interactively influenced by the serotonin transporter promoter region (5-HTTLPR) variation and childhood traumas (Stein, Schork, & Gelernter, 2008).

As stated in the epidemiology section, anxiety disorders are the most prevalent mental disorders in humans across lifespan. Considering that the largest proportion of variance in liability is explained by non shared environmental factor, a developmental psychopathology perspective is very useful to understand the possible origin of these disorders. Focusing on family characteristics, factors associated with an increased probability to trigger anxiety disorders are:

- Attachment. The nature of the attachment style may influence the cognitive, affective, behavioural, and physiological response of the infant to distressing or frightening situation, affecting the vulnerability to develop an anxiety disorder (Manassis, 2001). Mothers who had insecure adult attachments showed an insecure attachment to their children. Compared to the children with secure attachment, only those with insecure style had an anxiety disorder (Manassis, Bradley, Goldberg, Hood, & Swinson, 1994). Specifically, anxious/resistant attachment style doubled the risk to develop an anxiety disorder in late adolescence (Warren, Huston, Egeland, & Sroufe, 1997).
- Parental rearing style. According to the literature (Ballash, Leyfer, Buckley, & Woodruff-Borden, 2006), a parenting style characterized by over-control, low warmth, and rejection could contribute to the development of anxiety. Early experiences of parental over-protection might provide information to the child that the world is a threatening place, leading to hyper vigilance and fear. It also limits the development of successful coping strategies, and could affect an adequate sense of control and mastery over their environments (Seehagen, Margraf, & Schneider, 2014).
- Learning experiences. Especially in the field of learning theory it has been suggested that parents influence anxiety responses of the children through three learning mechanisms: parents

may reinforce anxious and avoidant behaviour in children by means of operant learning; children could learn how to cope and behave due to the observation of mother's and father's behaviours through vicarious learning (i.e, modeling); and by instructional learning (i.e., education) (Seehagen, Margraf, & Schneider, 2014).

Conversely, it was highlighted protective factors toward the development of anxiety in children are: the ability to inhibit behaviour when necessary (inhibitory control) and focus or shift attention (attentional control) (Muris, van der Pennen, Sigmond, & Mayer, 2008); a high level of perceived control or self-efficacy, and parental treatment for anxiety psychopathology (Chorpita & Barlow, 1998).

A great contribution to the experimental study of the aetiology of anxiety disorders arises from the learning theory. Many studies used experimental context conditioning procedure (in which an unconditioned stimulus was paired with a conditioned one) and provided support that patients with anxiety, and/or subjects with high vulnerability to anxiety disorders, are characterized by chronic apprehension of danger, a deficit in safety learning, a tendency to interpret ambiguous events in a negative fashion, and fear overgeneralization (Boddez, Baeyens, Hermans, & Beckers, 2014).

From cognitive perspective, patients with anxiety disorders are characterized by exaggerated threat appraisals: they tend to overestimate the costs of harm and to underestimate their own probability to cope with danger (Beck & Clark, 1988). Typically, these subjects also show maladaptive cognitive schemas, which in turn may lead to bias information processing, safety-seeking behaviour (such as dysfunctional coping strategies), and thought suppression or repetitive negative thinking (Beck & Clark, 1988).

From a neuroanatomical point of view, the attentional bias toward threat-related stimuli and the negative interpretation of emotionally ambiguous stimuli of subjects with anxiety disorders was

addressed to altered neural functions in specific brain regions (Mathews, Mackintosh, & Fulcher, 1997). Specifically, some of the brain structures here involved are:

- Amygdala. Many have suggested that the amygdala is involved in the perception and expression of emotions, particularly fear related negative affect and fear conditioning (Nees & Flor, 2014). When an anxious and fearful response is related to the presence of specific threatening stimuli, exaggerated amygdala reactivity was observed (Shin & Liberzon, 2010).
- Prefrontal cortex (PFC). Ventromedial PFC part are more involved in negative and positive emotional states while the dorsolateral part is more active during goal-oriented processing of emotional states (Nees & Flor, 2014).
- Anterior cingulate cortex (ACC). Activation of both dorsal and rostral parts of ACC occurred during fear conditioning and observational fear learning (Shin & Liberzon, 2010).

Other brain regions involved in anxiety are the orbitofrontal cortex (OFC), the insular cortex, the periaqueductal gray (PAG), the thalamus, the hypothalamus, and the striatum. This latter circuit, includes the regions described above, has been referred as the fear network (Nees & Flor, 2014).

An integrated model that summarizes the different perspectives on the aetiology of anxiety disorders was proposed by Barlow (2002) and goes under the name of the Triple Vulnerability Theory. According to his model, the odds for anxiety and related disorders are greatly increased when individuals possess three vulnerabilities (or diathesis): a generalized biological vulnerability, that refers to the genetically based, stable dispositions to experience to negative emotions that corresponds to core dimensions of temperament (e.g., neuroticism); the generalized psychological vulnerability in which early childhood stressful life-events, or inadequate parenting style, may inhibit the development of effective coping strategies and self-efficacy; and the specific psychological vulnerability that comes into play in the form of learning a particular focus of distress, or learning that some situations, objects, or internal states are potentially dangerous. The

co-occurrence of these three diathesis arises the probability to develop anxiety disorders (Barlow, 2002; Brown & Naragon-Gainey, 2013).

2. Panic

2.1. Panic attack

The etymology of the word “panic” derives from *panikòs* which means “of Pan”, the Greek demigod. According to the mythology, this creature lived in a forest and was peaceful, but if disturbed could issue a terrifying scream that caused to the unfortunate travelers a sudden reaction and an unmotivated terror (Barlow, 2002).

In clinical psychology and psychiatry, panic is described as an acute anxiety response that produced, due to a dysfunctional alarm system, an overwhelming emotional experience: the so called panic attack (PA) (Schmidt, Korte, Norr, Keough, & Timpano, 2014).

As reported in the current nosology, PA is a core characteristic, but not exclusive, of PD. Indeed, changes from the DSM-IV to DSM-5 have resulted in a different conceptualization of PA, which is now used as a specifier of the disorder. Therefore, panic attacks can occur in the context of any anxiety disorder as well as other mental disorders; it can also occur in the presence of certain medical conditions (e.g., cardiac, respiratory) or as a consequence of the use of drugs and psychoactive substances (APA, 2013; Craske et al., 2010).

As described in the DSM-5 (APA, 2013), a PA is characterized by an intense fear or discomfort that reaches a peak within minutes and is accompanied by four or more of the somatic and/or cognitive symptoms listed below (APA, 2013): palpitations, pounding heart, or accelerated heart rate; sweating; trembling or shaking; sensations of shortness of breath or smothering; feelings of choking; chest pain or discomfort; nausea or abdominal distress; feeling dizzy, unsteady, light-headed, or faint; chills or heat sensations; paresthesias; derealization or depersonalization; fear of losing control or “going crazy”; fear of dying.

The core aspect of PAs is given by neuro-vegetative symptoms, which can be divided into: cardiovascular (i.e., palpitations, tachycardia), respiratory (i.e., shortness of breath), gastrointestinal

(i.e., nausea or abdominal distress), and autonomic (i.e., alterations of thermal sensations, tremors). Psychological symptoms are mainly characterized by the fear of dying or going crazy, depersonalization, and derealisation. A panic attack in which fewer than four physical and/or cognitive symptoms are present is called *limited-symptom attack* (APA, 2013).

To describe the different types of PAs, the DSM-5 uses the distinction between "unexpected" and "expected". When PAs occur out of the blue, with no obvious cue or trigger (both internal or situational), they are *unexpected* (or spontaneous). A particular subtype is nocturnal PA, in which people are reawaken from sleep in a state of panic. On the other hand, *expected* PAs occur when an external cue, such as a feared phobic situation or stimulus, is associated with the induction of the panic response (Johnson, Federici, & Shekhar, 2014).

2.2. Panic Disorder

According to the DSM-5 (APA, 2013), panic disorder is characterized by recurrent and unexpected PAs, followed by a significant panic-related worry. Specifically, following at least one of the attack, a persistent concern about having additional PAs (e.g., losing control), worry about the consequences of PAs, or maladaptive changes in behaviour aimed to eliminating the risk of another attack, must be present for one month or more. To meet the diagnosis of PD, PAs cannot arise solely from the direct physical effects of a substance (e.g., medication) or from a medical condition (e.g., cardiopulmonary disorder); and cannot also be caused by other mental disorder (e.g., social anxiety disorder) (Schmidt et al., 2014).

An important change from DSM-IV-TR (APA, 2000) to DSM-5 (APA, 2013) is the unlinking of PD and agoraphobia. The former diagnoses of PD with agoraphobia, PD without agoraphobia, and agoraphobia without history of PD are now replaced by two diagnoses: PD and agoraphobia, each having separate diagnostic criteria. Indeed, as demonstrated by European researchers (Faravelli,

Cosci, Rotella, Faravelli, & Catena Dell'Osso, 2008), agoraphobia could be present without any prior indication of panic or panic-like symptoms.

PAs can be moderately frequent (i.e., once a week) or occur in short series (i.e., daily), but spaced by weeks or months without any panic-like manifestation. PAs can also be less frequent (i.e., every two months), but occurring for many years. In terms of severity, subjects with PD can have either full-symptoms (with four or more symptoms criteria) or limited-symptom attack (with less than four symptoms) (APA, 2013).

2.3. Epidemiology of panic attack and panic disorder

The percentage of people who have experienced a panic attack is very high. According to an epidemiological study (Kessler, et al., 2005$_a$; Kessler, Chiu, Jin, Ruscio, Shear, & Walters, 2006), the prevalence rates for at least one PA during the life was 28.3%; while, panic attack prevalence rates within the last year was around 11%. No significant differences were observed in twelve-month prevalence rates among African Americans, Asian Americans, and Latinos. For European country, the 12-month prevalence rates of PA was lower, ranging from 2.7% to 3.3% (APA, 2013).

Concerning PD, lifetime prevalence ranges from 4.7% to 5.1%. The 12-month prevalence of PD was around 2.1%-2.8% (Kessler, et al., 2006).

Results from an epidemiological study on the Italian population (De Girolamo et al., 2006) showed much lower prevalence rates of PD compared to the other European and non-European country (1-month prevalence rates: 0.1%-0.3%; 12-months: 0.4%-0.8%; lifetime prevalence: 1.6%). Similar results were obtained from The Sesto Fiorentino Study (one-year total prevalence rate for PD: 1.4%; one-year women prevalence rate: 1.9%; one-year men prevalence rate: 0.7%) (Faravelli et al., 2004).

PAs seem to be more common that PD and have elevated comorbidity with other psychiatric condition (i.e., other anxiety disorders and mood disorders) (Kessler, et al., 2006).

Women have shown a significantly higher risk to develop PA and PD compared to men (rate 2:1) (APA, 2013; Kessler, et al., 2006). PAs can occur during puberty, whereas they are relatively rare during childhood; also for PD the prevalence rate was found higher after 14 years of age, showing a peak during adulthood. Specifically, the highest prevalence rate was around 6% in individuals from 30-to-64-years of age, and around 2% for 65 years and older age group (APA, 2013).

2.4. Aetiology of panic

The aetiology and pathogenesis of panic is complex and has been extensively studied both from a genetic, biological, neuroanatomical, and psychological point of view (Hettema, Neale, & Kendler, 2001; Gorman, Kent, Sullivan, & Coplan, 2000; Bouton, Mineka, & Barlow, 2001). Studies on genetics of PD have produced mixed results that are inconsistent, negative, or not clearly replicated, thus the exact genes and polymorphisms associated with panic remains unknown and requires further elucidation (APA, 2013; Maron & Shlik, 2014).

The Suffocation False Alarm theory (SFA) (Klein, 1993) hypothesized the presence of an evolved physiologic suffocation alarm system which monitors information about potential suffocation stimuli. According to Klein, subjects with panic possess an hypersensitive suffocation system that produces false suffocation alarms (i.e., panic attack) (Preter & Klein, 2008). As a support to Klein's theory, dyspnea is a core symptom of panic attack (McMillan & Rachman, 1988). This hypothesis has been also supported by studies using biological challenges, such as inhalation of high concentrations of carbon dioxide (see paragraphs 2.6.3).

One of the most comprehensive neuroanatomical theories of PD is the Neuroanatomical Hypothesis proposed by Gorman and colleagues (2000). They postulated the presence of a fear network in the brain that mediates the behavioural symptoms of PD. The major brain structures involved in this fear network is the amygdala, but it also includes the prefrontal cortex, insula, thalamus, and amygdala projections to the brainstem and hypothalamus (Fava & Morton, 2009).

This theory suggests that patients with panic present an extremely low threshold for the activation of the fear network in the brain and that an excessive activity in this network leads to autonomic and neuroendocrine activation, responsible for the typical PD symptoms (Fava & Morton, 2009).

Early traumatic life events (i.e., death of the parents or sexual abuse during childhood) (Goodwin, Fergusson, & Horwood, 2005), parental attitudes or child-rearing styles characterized by overprotection and neglecting (Bandelow, Späth, Tichauer, Broocks, Hajak, & Rüther, 2002), and cigarette smoking (Cosci, Knuts, Abrams, Griez, & Schruers, 2009) represent the most studied environmental risk factor associated with the development of PD (APA, 2013).

According to psychodynamic theory, panic is the result of an unconscious sexual conflict, due to the accumulation of sexual tension (Michels, Frances, & Shear, 1985). More recently, the psychoanalytic perspective has extended its vision considering anxiety as the result of any form of underlying conflict (Sweeney & Pine, 2004). However, the psychological theories with higher clinical and scientific evidence are those of the cognitive and behavioural perspective.
In the following paragraphs, will be presented.

2.5. Psychological theory of panic

According to Clark's, who formulated the Catastrophic Misinterpretation theory (1986), people with recurrent PAs cognitively and catastrophically misinterpret their bodily sensations as evidence of impending danger. For example, people with panic might perceive their shortness of breath as a signal of suffocation; palpitations or tachycardia, that could arise in daily events (i.e., physical exercise) or be caused by non-anxiety-related emotional states (i.e., excitement or anger). This symptom might be misinterpreted as a signal of a heart attack and impending loss of control (Fava & Morton, 2009). Clark described the vicious circle through which the PA occurs (1986): external (i.e., a crowded supermarket) or internal stimuli (i.e., bodily sensations, a thought) are perceived as a threat and they lead to a state of apprehension. This state is followed by the

emergence of new bodily sensations that, if evaluated in a catastrophic fashion, continued to increase the state of apprehension, which produce other or more intense physical symptoms until the “explosion” of a PA.

A number of studies have provided evidence of the great tendency in panic patients to catastrophically misinterpret their sensations (Khawaja & Oei, 1998). Studies that have used threatening-word task (Casey, Oei, & Newcombe, 2004; Maidenberg, Chen, Craske, Bohn, & Bystritsky, 1996) showed that PD subjects had a higher response time specifically for panic words (not for emotional positive one), compared to healthy subjects or those with other psychiatric disorders. Further evidence comes from studies sustained that improvement in panic disorder depends on the reduction of catastrophic misinterpretation of bodily sensations, and successful treatment is characterized by a reduction in cognitive threat bias at post-treatment and at follow-up, compared to treatment not specifically design to reduce catastrophic cognition (Westling & Ost, 1995). However, Clark’s theory seems to fail to explain how PAs occur even in the absence of detectable catastrophic cognitions, such as during nocturnal sleep (Bouton et al., 2001). Clark (1988) has hypothesized the presence of an “unconscious" catastrophic misinterpretation, thus subjects might monitor, detect, and catastrophically misinterpret their sensation even during sleep, awaking in the middle of a full-blown attack (Clark, 1988).

Bouton and colleagues (2001) highlighted that catastrophic cognitions often accompany PAs and suggested that such cognitions contribute to panic symptoms acting as conditioned stimuli. They proposed that the exposure to panic attacks might cause the conditioning of panic to exteroceptive and interoceptive cues. As a result, even mild panic-like symptoms (e.g., breathlessness, palpitations) may be perceived as a warning cue that trigger a full-blown attack. Consistently with this hypothesis, Barlow (1991) underlined that PA is essentially a fight or flight response in the absence of a real danger, causing a false alarm. This false alarm is followed by

increased arousal, self-focused attention related to the possibility to experience further PA, and the belief that the attacks are dangerous.

An influential theory which has inspired several scientific works on anxiety is the Anxiety Sensitivity theory (Reiss & McNally, 1985; for more details see paragraphs 3).

The AS theory posits the existence of a personality trait, anxiety sensitivity (AS), characterized by the belief that anxiety and its related sensations, especially somatic symptoms, are highly dangerous yielding adverse physical, psychological, and social consequences (McNally, 1994). Individuals with high AS may believe that breathless is a signal of suffocation or that palpitations indicate a heart attack, while those with low AS experience these sensations as undesirable, but not threatening (Schmidt et al., 2014).

The AS theory differs from the interoceptive conditioning theory because, according to Barlow (1991) and Bouton et al. (2001) PD development is referred to a pattern of conditioned responses to internal stimuli, whereas AS focuses on the belief that anxiety symptoms, and, their associated sensations, are dangerous. The AS theory is also different from the catastrophic misinterpretation theory by Clark (1986) because it has underlined that PD patients are aware of the causes of their sensation and anxiety symptoms are common and physiological (i.e., PD subjects do not misinterpret symptoms).

2.6. Panic-like symptoms: laboratory triggers

Experimental studies on panic have been long used a retrospective and subjective approach due to the unpredictable nature of PAs. To build methodologically and effective study on PD, researchers have implemented experimental procedures able to reproduce panic under controlled laboratory conditions. In general, there are three types of approach to induce panic: the pharmacological, the physiological, and the psychological one (Cosci et al., 2004).

Laboratory triggers are considered valid when they are able to accurately reproduce the symptoms of spontaneous PAs; when the test response is specific only for PD patients or subjects vulnerable to panic compared to healthy subjects; when the phenomena is short-lived or readily reversible; when clinically effective drugs for PD treatment reduce the response to the challenge; when the results can be replicated (Guttmacher, Murphy, & Insel, 1983; Gorman, Fyer, Liebowitz, & Klein, 1987).

The most used pharmacological laboratory triggers to induce panic-like symptoms are: lactate (Wemmie, 2011; Liebowitz, et al., 1984), cholecystokinin (CCK) (Bradwejn & Koszyck, 1994), yohimbine (Charney, Woods, Goodman, & Heninger, 1987), and caffeine (Charney, Heninger, & Jatlow, 1985).

The psychological approach widely used refer to behavioural and cognitive methods, such as exposure to phobic or painful stimuli (Bystritsky, Maidenberg, Craske, Vapnik, & Shapiro, 2000), or exposing subjects to read writings that evoke their fears (Teachman, Smith-Janik, & Saporito, 2007).

The physiological approach affects the respiratory system, causing suffocation. The most commonly used challenges are carbon dioxide (CO_2) inhalation (Griez, Lousberg, van den Hout, & van der Molen, 1987; Verburg, Perna, & Griez, 2001), hyperventilation (Maddock & Carter, 1991), and the Breath-Holding test (Zandbergen, Strahm, Pols, & Griez, 1992).

2.6.1. Pharmacological triggers

The sodium lactate was the first panicogenic challenge to be studied. Thanks to Pitts and McClure (1967), who firstly used lactate for panic induction in the laboratory, it was hypothesized that this dissociated cationic form of lactic acid could elicit panic-like symptoms in vulnerable individuals. They observed that 13 out of 14 subjects with anxiety neurosis, and only 2 out of 10 healthy controls, reported symptoms of panic after the infusion of sodium lactate (Pitts & McClure, 1967; Esquivel, Schruers, & Griez, 2008).

The mechanism behind lactate-induced panic remains unclear. Early studies proposed the involvement of peripheral and central adrenergic surge or metabolic alkalosis (Liebowitz, Gorman, Fyer, Dillon, Levitt, & Klein, 1986); more recently, it was proposed that sodium lactate affects the respiratory centre with a secondary activation of brain noradrenergic systems (Nutt & Lawson, 1992). Basically, lactate infusions produces hypercapnia, thus inducing a paradoxical hyperventilation which causes a reduction of CO_2 in the blood (i.e., respiratory alkalosis and impaired balance acid-base) (Liebowits et al., 1984).

The efficacy of sodium lactate as panicogenic laboratory challenge has been demonstrated by numerous studies, in which patients with PD were significantly more prone to panic compared to healthy subjects, or patients with other psychiatric disorders, such as depression, OCD, SP or bulimia (Liebowits et al., 1984). Although less intense than in PD patients, panic responses were also observed in patients with generalized anxiety disorder (Cowley, Dager, McClellan, Roy-Byrne, & Dunner, 1988), premenstrual dysphoric disorder (Facchinetti, Romano, Fava, & Genazzani, 1992), and post-traumatic stress disorder (Jensen et al., 1997). Cowley and Arana (1990) reported that panic induced by lactate had a sensitivity of 67% and a specificity of 89% in differentiating patients with panic disorder from control groups.

Limits of sodium lactate challenge are related to the intensity of provoked anxious response. When the elicited symptoms are too heightened, the interruption of the test is quite likely, resulting in high drop-out rates and raising ethical concerns. Moreover, it is possibile to assume that only subjects who get into a little intense anxiety response can complete the challenge procedure (Cosci et al., 2004).

Another widely used panicogenic challenge is the cholecystokinin. It is a common neurotransmitter and produces excitatory effects on brain regions that are implicated in the generation of panic symptoms, such as the limbic area and the brain stem (Bradwejn & Koszyck, 1994). Study on rodents showed that mice exposed to a stressor present a higher level of

tetrapeptide form of CCK (CCK-4) compared to control group (Harro, Kiivet, Lang, & Vasar, 1990; Pavlasevic, Bednar, Qureshi, & Sodersten, 1993). In humans, the first infusion of CCK-4 as a panicogenic challenge was carried out by de Montigny (1989), who demonstrated that CCK-4 induces anxiety in healthy volunteers. Additional studies confirmed that the administration of CCK-4 induces PAs in PD patients, but also that the administration of anti-panic drugs reduced the intensity of the provoked panic symptoms (Bradwejn et al., 1994). Selective serotonin reuptake inhibitors (SSRIs) reduce the panicogenic effect of CCK-4 in patients with PD (Shlik, Aluoja, Vasar, Vasar, Podar, & Bradwejn, 1997).

Evidence has been found for the interactions and co-localization of CCK with several neurotransmitters, such as dopamine, 7-aminobutyric acid (GABA), serotonin (5-hydroxytryptamine; 5-HT), noradrenaline, excitatory amino acids, and opioid peptides (Van Megen, Westenberg, den Boer, & Kahn, 1996).

In an experimental study on PD patients, Ströhle and colleagues (2000) observed that the administration of CCK-4 stimulated the adrenocorticotropic hormone (ACTH), whereas cortisol concentrations remained unaffected. Increased in ACTH and cortisol secretion after CCK-4 administration was also observed in healthy subjects and individuals with panic-like symptoms. Limitations of this procedure are related to: poor specificity in detecting panic, because a large percentage of subjects without PD respond to the test; lack of standardized guidelines, concerning the administration methods and the doses to be used (which make difficult to compare different studies) (Cosci et al., 2004).

Caffeine is an adenosine receptor antagonist, a neuromodulator that influences the noradrenergic system, which indirectly increases norepinephrine and arousal. Caffeine is widespread used as a stimulant, for example in the medical field it is administered to avoid sleepiness or treat the headache, but it also increases alertness and attention (Nehlig, Daval, & Debry, 1992). Caffeine administration has been used as a laboratory challenge to reproduce panic

manifestation since it significantly increases anxiety, nervousness, fear, nausea, palpitations, agitation, and/or tremors in patients with PD (Charney et al., 1985; Vilarim, Rocha Araujo, & Nardi, 2011). The specific mechanism underlying the caffeine panicogenic effects remains unknown, although the most likely pattern is considered to be the antagonism of central adenosine receptors (Nardi et al., 2008).

Although caffeine has been extensively used for the study of panic, its effect is non-specific and most probably associated to generalized anxiety than to panic. Moreover, research using caffeine as a model of panic has been scarce and no clinical validation studies have been performed (Esquivel et al., 2008).

2.6.2. Psychological triggers

Psychological triggers for PA are substantially based on behavioural and cognitive methods. Behavioural approach has long been used the exposure to phobic (i.e., public speaking) or painful stimuli (i.e., electric shock), referring as a theoretical basis to the classical conditioning theory (Wolpe & Rowan, 1988). A wide used method to induce subjective anxiety is the Trier Social Stress (TSS) test developed by Kirschbaum and colleagues (1993). The TSS test simulates a job interview, in which participants are instructed to imagine and role-play their dream job examination. The TSS test is composed by three successive phases: a) preparation period (3 minutes), b) a free speech task in which the participants have to argue why they are the best candidate for the job they wish to apply for (5 minutes), and c) a mental arithmetic task (5 minutes). The tasks are performed in front of a selected committee, providing no facial or verbal feedback. Participants are also video-taped and are informed that their performance will be evaluated (Frisch, Häusser, & Mojzisch, 2014). The TSS test has been found to reliably activate the hypothalamic–pituitary–adrenal (HPA) stress axis and leads to high levels of self-reported stress and anxiety (Kudielka, Hellhammer, & Kirschbaum,

2007; Hellhammer & Schubert, 2012). However, the level of anxiety provoked by this task is related to the extent to which they can tolerate the social pressure and embarrassment.

Cognitive approach has predominantly involved guided imagery process (Bystritsky et al., 2000) and recently virtual reality exposure (De Carvalho, Freire, & Nardi, 2010). Bystritsky and colleagues (2000) have used an imagery task to expose patients to a panic provoking situation and examine their reactivity to imagined threatening stimuli. When images of noxious and phobic information were presented, an increase of physiological reactivity were observed in patients with phobia; whereas, few significant differences were observed between the panic group and healthy controls, after taking into account differences at baseline. Thus, imagery exposure may not be strong enough to evoke panic as triggered by specific situations and it may be also difficult to find a clear frightening image for panic subjects (Freire, De Carvalho, Joffily, Zin, & Nardi 2010).

An innovative technique to induce panic in PD patients is the computer stimulation (Ling, Nefs, Morina, Heynderickx, & Brinkman, 2014). Virtual reality (VR) is becoming more realistic, allowing researchers to have a higher control and to experiment novel therapeutically approaches (Freire et al., 2010). VR allows the simulation of different real situations in a tridimensional computer-generated environment, in which people can elicit a similar anxiety response than a real phobic situation (Botella et al., 2007). Freire and colleagues (2010), investigating if a VR bus trip could induce anxiety and physiologic alterations in patients with PD and agoraphobia, they observed a significant difference for skin conductance, electrodermal response magnitude, respiratory rate, and respiratory rate irregularity compared to healthy controls. As a further evidence, a recent review of the literature showed that VR represent a valid and efficacy exposure method to evoke psychophysiological arousal, especially in terms of electrodermal activity in patients with anxiety disorders (Diemer, Mühlberger, Pauli, & Zwanzger, 2014).

2.6.3. Physiological triggers

2.6.3.1. The CO_2 challenge

The CO_2 inhalation has been extensively used as a safe and noninvasive challenge procedure to induce panic attacks in PD patients in preclinical and clinical research laboratory settings. The panic-like symptoms induced by the CO_2 produce short-lived effect, similar for duration, severity, and type to a real PA (Verburg et al., 2001). In a recent review, Amaral and colleagues (2013) underlined that CO_2 challenge allows investigators to test the validity of the SFA theory (Klein, 1993) and to study the sensitivity to hypercapnia, discriminating between PD patients who experience more respiratory symptoms *versus* non-respiratory symptoms. The CO_2 challenge has been also used to examine the sensitivity of healthy relatives of PD patients, and other vulnerable individuals (i.e., high level of anxiety sensitivity subjects), and to verify the ability of anxiolytic drugs to prevent, eliminate, or reduce CO_2 sensitivity (Amaral, Spadaro, Pereira, & Nardi, 2013). CO_2 elicits its panicogenic effect increasing the pCO_2 in the blood (hypercapnia) and diminishing pH (respiratory acidosis) thus, stimulating the chemoreceptors to raise the respiratory frequency and producing the typical panic symptomatology (i.e., dizziness, breathlessness, etc.) (Wemmie, 2011). Carbon dioxide and its relation with anxiety was experimentally studied for the first time by Cohen and White (1951) in 43 patients with neurocirculatory asthenia (currently, the equivalent of panic disorder) and 27 control subjects who underwent an oxygen rebreathing for twelve minutes, and then 4% CO_2 rebreathing for twelve minutes. They observed an increase of sighs to a mean of 7.5 per twelve-minute in PD patients, compared to a mean of 2.8 in healthy controls. The 46.5% of patients reported that the symptoms occurred were equal to their real “anxiety attack”; patients also referred other symptoms, such as “feeling of fear” which were not reported by controls. Cohen and White’s discovery has been put aside until 1980, when two independent groups started using carbon dioxide as panicogenic challenge. From one side, Gorman and colleagues (1984) reported that 5% CO_2 hyperventilation was associated with more panic-like symptoms compared to the simple

hyperventilation procedure in patients with PD. On the other side, Griez and Van den Hout (1984) observed that a single inhalation of 35% CO_2 causes a strong autonomic response in all subjects, reproducing a PA. Specifically, CO_2 triggers an immediate feeling of anxiety in PD patients. The irony is that Griez and Van den Hout (1984) were searching for a method to reduce anxiety, to teaching patients to cope with an imminent anxiety attack through the exposure paradigm of behaviour therapists. Conversely, they found a laboratory method to induce anxiety symptoms (Verburg et al., 2001). From the results of these early studies, a growing body of research using CO_2 as a safe, non-invasive, and effective laboratory challenge to induce panic-like symptoms have been conducted.

The main criterion to declare that a PA occurred after CO_2 inhalation is: a) the occurrence of fear or panic; b) the presence of at least 4 neuro-vegetative symptoms among the specified for PA in the DSM, including c) at least one of the DSM cognitive symptoms (i.e., fear of dying, going crazy, or losing control) (Perna, Cocchi, Bertani, Orange, & Bellodi, 1995; Sanderson, Rapee, & Barlow, 1989). However, many researchers use more strict criteria. For example, Nardi and colleagues (2006) added as criterion that the patients describe the PA provoked by CO_2 as resembling the real-life PAs, and that two medical doctors agree that the patient had a clinical PA. An increase of at least 26% at the VAAS (Visual Analogue Scale of Anxiety) was suggested by other authors (Perna, Bertani, Caldirola, & Bellodi, 1996).

When the CO_2 challenge was preceded by the administration of benzodiazepines (Sanderson, Wetzler, & Asnis, 1994; Woods, Charney, Loke, Goodman, Redmond, & Heninger, 1986), tricyclic antidepressants, or SSRI (Bertani, Perna, Arancio, Caldirola,& Bellodi, 1997; Pols, Hauzer, Meijer, Verburg, & Griez, 1996), a reduced panicogenic effects of the challenge was observed. The same result was found in case of administration of non-pharmaceutical approaches, specifically physical exercise (Esquivel, Diaz-Galvis, Schruers, Berlanga, Lara-Munoz, & Griez, 2008; Smits, Meuret, Zvolensky, Rosenfield, & Seidel, 2009), CBT (Meuret, Rosenfield, Hofmann,

Suvak, & Roth, 2009; Schmidt, Trakowski, & Staab, 1997), or in case of alcohol intake (Cosci, De Gooyer, Schruers, Faravelli, & Griez, 2005).

Number of studies on twins (Bellodi, Perna, Caldirola, Arancio, Bertani, & Di Bella, 1998), and relatives of PD patients (Coryell, Pine, Fyer, & Klein, 2006) who underwent CO_2 challenge provided evidence for the existence of a genetic marker in PD, compared to healthy control who showed a very low susceptibility to hypercapnia (Harrington, Schmidt, & Telch, 1996).

In the following paragraphs the three main laboratory procedures to administer the CO_2 challenge are presented.

2.6.3.1.1. Continuous exposure procedure

CO_2 can be administered in a continuos exposure, via two procedures: the Steady-State breathing and the Read rebreathing techniques (Abrams, Schruers, Cosci, & Sawtell, 2008).

In the Steady-State breathing procedure, subjects continuously breathe a steady-state level, generally 5% or 7% CO_2 gas mixture for a set period of time, usually 10 or 20 minutes, or until the occurrence of PA. CO_2 is administered with subject's head enclosed in a clear plastic respiratory canopy, in supine position. The canopy is completely sealed, but allowed participants to see and hear (Gorman et al., 1984). Usually, the effects of CO_2 begin after few minutes of inhalation and disappear at the end of the procedure (Sanderson & Wetzler, 1990).

Steady-State breathing procedure should be used carefully; indeed, as stated by Sanderson and Wetzler (1990), debriefing interviews on experimental subjects have revealed that the respiratory canopy increases the likelihood to feel "suffocated" or "trapped". This aspect could be an advantage if the aim is to provoke PAs, but it constitutes a disadvantage if the aim is to study the anxiogenic properties of CO_2 (Abrams et al., 2008; Sanderson & Wetzler, 1990).

In the Read rebreathing approach (Read & Leight, 1967), CO_2 mixture is inhaled and exhaled into a close system. The procedure starts using the 5-7% CO_2 concentrations; then, the percentage of CO_2

in the system is gradually increased and the participant continuously breaths in and out from the system through an oral mask, typically reaching levels 2–3% higher within 5 min (Abrams et al., 2008). Numerous experimental data suggested that the intensity of panic symptoms provoked by CO_2 are contingent upon the dose administered. Gorman and colleagues (1988) observed that if the initial concentration of CO_2 was 5%, the 29% of PD patients and the 6% of controls experienced PAs, while if the initial concentration of CO_2 was 7%, PD patients and controls that experienced a PA rose to 68% and 12%, respectively. Therefore, the larger dose of CO_2 is invariably related to a higher panic rate in PD patients (Esquivel et al., 2008; Nardi et al., 2006).

The advantage of Read rebreathing approach (Read & Leight, 1967) is related to the possibility of studying physiological, psychological, and behavioural changes due to the different amount of inspired CO_2, during the same experimental session. The limitation of this method is that, with increasing levels of CO_2, early termination due to the panic manifestation becomes more likely, and comparisons of pre- to post-challenge across participants become more challenging to interpret (Abrams et al., 2008).

2.6.3.1.2. Double and single inhalation of CO_2

The most widely used techniques to administer CO_2 are single or double inhalation. Subjects are invited to take one or two vital capacity of breath of CO_2 mixture of 35% CO_2 and 65% oxygen concentration by means of a nasal-oral face mask.

In line with the protocol for 35% CO_2 inhalation used at the Maastricht Academic Anxiety Center (Verburg et al., 2001), immediately before and after each inhalation (the CO_2 challenge and the placebo mixture), subjects are invited to fill few psychological instruments. Commonly used instruments are the Panic Symptom List (PSL; APA, 2000), a list composed of the 13 criteria for PA of DSM-IV-TR (APA, 2000), whose score can be considered an index of global symptoms reaction to the CO_2 challenge; the Visual Analogue Scale of Anxiety (VAAS), the Visual Analogue Scale of

Fear (VAS-F), and the Visual Analogue Scale of Discomfort (VAS-D) (Gift, 1989) that evaluate the level of subjective anxiety, fear, or discomfort, respectively. They are assessed on a continuous line from 0 mm (no anxiety, no fear, or no discomfort) to 100 mm (the worst anxiety, fear, or discomfort). Psychophysiological measures are also collected: the most used are the respiratory rate, the partial pressure of arterial CO_2 (pCO_2), the heart rate, the blood pressure, the skin conductance, and the salivary cortisol level (Papp et al., 1997).

Compared to the Steady-State breathing and the Read rebreathing techniques, double or single inhalation have the advantage to be the fastest and easiest procedure to induce hypercapnia and its related symptoms, with the briefest duration (Verburg et al., 2001). Another advantage of these techniques are a lower probability of losing participants to machine malfunction, more participants can be run in a fixed time period, and premature challenge termination rarely occurs (Abrams et al., 2008).

Although the 35% CO_2 challenge is fairly simple, a number of important issues should be considered. The panicogenic effects must be due to the inhalation of CO_2. Alternative explanations suggest that the laboratory setting, the role of the investigators, the machinery, or the instruction may induce or manipulate the level of anxiety experienced by the subjects. To avoid this methodological biases, each experimental or control subjects receives standardized instruction before undergoing the CO_2 challenge. Such instructions inform the participants that they may experience some level of anxiety and physical symptoms and, as stated by Verburg and colleagues (2001), “in the procedure of the 35% CO_2 challenge, the word panic is deliberately not mentioned” (p.348).

Another methodological maneuver is the use of placebo condition; according to a double blind and randomized order, each subject takes a breath of 35% CO_2 and 65% oxygen gas mixture and a breath of 80% N_2 and 20% O_2, almost the composition of normal air (the placebo condition). To be

considered valid, the CO_2 and placebo gas mixture inhalations need to be equal to the 80% of the subject's vital capacity of breath (Verburg et al., 2001).

2.6.3.2. Voluntary hyperventilation procedure

Voluntary hyperventilation consists in doing extra breathing compared to the metabolic needs. Hyperventilation removes CO_2 from the lungs and produces a decrease of the partial pressure of arterial CO_2 (pCO_2). The reduction of pCO_2 below 35 mm/Hg is defined as hypocapnia. Consequently, cerebral blood flow is reduced and the lactic acid increases causing hypercapnia and respiratory alkalosis (when pH exceeds 7.45) (Abrams et al., 2008; Esquivel et al., 2008). When hyperventilation is used as a biological challenge procedure, the subjects are invited to breath every 2 seconds for durations ranging from 3 to 15 minutes (Abrams et al., 2008). An audio-recorded instruction can also be used to standardize the rhythm of breathing and assess subjects' compliance (Zvolensky et al., 2004). The level of anxiety, respiratory rate, and heart rate are typically evaluated at baseline and 1 minute and 5 minutes after the end of the challenge-test (Nardi et al., 2004). Symptoms induced by hyperventilation are very similar to a panic attack and may include dizziness, paresthesias, palpitations, dyspnea, tachycardia, sweating, and feelings of unreality (Abrams et al., 2008).

Early studies proposed that hyperventilation can cause PAs. In favour of this hypothesis, it was shown that PD patients had panic symptoms while hyperventilating (Rapee, Brown, Antony, & Barlow, 1992; Freire & Nardi, 2012) and those who experience more respiratory symptoms during a PA react more to the hyperventilation test (Nardi et al., 2004) as well as those who having "habit" of rapid breathing (Barlow, 2002). On the other hand, an overwhelming body of evidence indicated that hyperventilation cannot be considered a cause of PAs and that it is a poor panicogenic challenge (Esquivel et al., 2008). Goetz, Klein, Papp, Martinez and Gorman (2001) reported that hyperventilation triggers PAs in 16% of PD, while CO_2 inhalation triggers PAs in 66% of cases.

Thus, although PD patients are more vulnerable to hyperventilation challenge compared to patients with GAD or social anxiety, hyperventilation seems to be less specific and effective in inducing panic than other challenge procedures, such as CO_2 inhalation (Abrams et al., 2008; Esquivel, Schruers, Maddock, Colasanti, & Griez, 2010; Goetz et al., 2001).

2.6.3.3. The breath-holding test

The breath-holding (BH) test is a standardized challenge procedure used to induce panic-like symptoms under controlled laboratory conditions; it produces an endogenous increase of CO_2 and, thus, respiratory acidosis (Cosci, Bertoli, & Abrams, 2013). The standard procedure (van der Does, 1997) consists of 4 attempts of apnoea. During the first three attempts, participants are invited to hold their breath following a normal exhalation and to maintain the cessation for as long as possible. These first three attempts have one minute anticipation period, followed by cessation of breathing at functional residual capacity, followed by a recovery period of two minutes. During the fourth trial the subjects are asked to inhale at the maximum vital capacity. The duration of maximal breath holding had been thought to reflect tolerance to CO_2 or physical sensations, with shorter times reflecting lower tolerance (Abrams et al., 2008). Typically, physiological parameters and the level of anxiety are evaluated immediately before and after the challenge.

Some studies have investigated the efficacy of BH test in inducing PAs (Nardi, Nascimento, Valença, Lopes, Zin, Mezzasalma, & Versiani, 2002; Nardi, Nascimento, Valença, Lopes, Mezzasalma, & Zin, 2003; Nardi et al., 2006). Nardi and colleagues (2002) compared PD patients, their first-degree relatives, and healthy controls on BH challenge to verify if they respond in a similar way to the induction of PAs. The authors observed that PD patients are significantly more prone to develop PAs as a response to the BH test (46%) compared to first-degree relatives (7%), and healthy control (4%). The data suggested that the BH test is a marker for PD patients, especially those with more prominent sensitivity to hypercapnia (the “respiratory subtypes”).

3. Anxiety sensitivity

The interest toward anxiety sensitivity (Reiss & McNally, 1985) is related to three main reasons: a) AS plays an important role in the genesis and maintenance of anxiety disorders, specifically for PD; b) longitudinal, experimental, and psychometric research have consistently supported its central role in the aetiology of anxiety; c) treatments specifically designed to reduce anxiety sensitivity increase the healing and prognosis of PD (Taylor, 2014).

As briefly described in paragraph 2.5, AS is the fear of anxiety-related bodily sensation, due to the belief that they are psychologically, physiologically, and socially harmful (McNally, 2002; Reiss & McNally, 1985). Individuals with high AS experience heightened fear in response to anxiety-inducing stimuli and find their anxiety symptoms as aversive. For example, subjects with high AS may be frightened of harmless heart palpitations, because they believe the sensations will lead to cardiac arrest, whereas individuals with low AS do not fear these sensations because they believe they are innocuous (Zvolensky & Schmidt, 2007).

The most used instrument for measuring AS is the Anxiety Sensitivity Index (ASI; Reiss, Peterson, Gursky, & McNally, 1986; Peterson & Reiss, 1992). The ASI is a self-report questionnaire, composed of 16 items with a response format on a 5-point Likert scale (from 0 “very little” to 4 “very much”). Originally, AS was presented as a one-dimensional construct (McNally, 1996), but additional studies on the psychometric and factorial properties of ASI have suggested a multidimensional structure, consisting of separate and distinct factors (Lilienfeld, 1996). Specifically, AS is composed of a unifactorial structure at the higher order level and by a multifactorial structure at the lower order level (Taylor, 1999). Factor-analytic studies showed that the three most reliable lower order factors of AS are: 1) fear of physical symptoms (i.e., beliefs that anxiety-related physical sensations as signs of imminent physical catastrophe), 2) fear of publicly observable anxiety symptoms (i.e., beliefs that publicly-observable anxiety sensations as signs of

imminent public embarrassment), and 3) fear of cognitive dyscontrol (i.e., beliefs that anxiety-related psychological sensations as signs of imminent mental breakdown) (Taylor, 1999).

AS is a dispositional variable, empirically and conceptually distinct from trait anxiety (McNally, 2002). Indeed, trait anxiety, as a higher order construct, is referred to a general tendency to respond fearfully to stressor, while AS, as a lower order construct, is a fear of experiencing anxiety symptoms (Taylor, 2014). The two constructs are independent and can occur in the same person in different ways: individuals may have high levels of trait anxiety (as the tendency to experience frequent and intense episodes of anxiety), but low AS (they are not afraid of anxiety itself), and vice versa (McNally, 2002; Taylor, 2014).

AS is also distinct from catastrophic misinterpretation theory (Clark, 1986), since it is not necessary that a person misinterpret his own bodily sensation to panic (McNally, 1990).

According to Schmidt, Lerew, & Joiner (2000), who demonstrated the validity of the Scar model, the experience of PA may worsen and increase the levels of AS, but growing evidence have also shown that elevated AS precedes the occurrence of panic (Korte, Brown, & Schmidt, 2013; Li & Zinbarg, 2007) providing additional support for the Predisposition model (Schmidt et al., 2000). Therefore, AS is currently considered one of the factors involved in the development of anxiety disorders; specifically, AS is considered a cognitive risk factor for panic, which in turn could affect AS in its intensity (Taylor, 2014). Reiss & McNally (1985) believed that the AS might present a genetic basis, and that it could be also acquire through learning experience, attachment, and parenting style. The first study on heritability of anxiety sensitivity was conducted by Stein and colleagues (1999) who enrolled 179 monozygotic and 158 dizygotic twin pairs. They found that AS has a strong heritable component, accounting for almost half of the total variance in AS scores. The authors also found that shared environmental factors accounted for the 11% of variance in the psychological concerns factor of AS, suggesting that important aspects of this component are influenced by family environment. In a subsequent analysis of the same sample, Jang and colleagues (1999) observed that AS factors were heritable only in women, accounting for 37% to

48% of the total variance. In children, it was observed a large genetic overlap between AS and anxiety symptoms (Waszczuk, Zavos, & Eley, 2013) and both anxiety and depressive symptoms in adolescence (Zavos, Rijsdijk, Gregory, & Eley, 2010).

A specific genetic vulnerability factor for AS has not been identified yet, but a strong candidate might be related to the polymorphism in the promoter of the serotonin transporter gene (Stein et al., 2008).

Regarding the developmental antecedents of AS, Watt and colleagues (1998) examined if childhood operant and vicarious learning experiences predicted AS in a retrospective study conducted in university undergraduates. They also compared if childhood operant and vicarious learning experiences varied among students with high, moderate, and low AS. They observed that parental reinforcement of sick-role behaviour in response to childhood anxiety symptoms, the exposure to uncontrolled parental behaviour (e.g., alcoholism or aggression), and the exposure to parental sick-role behaviour in response to parents' own anxiety symptoms, predicted AS (Watt, Stewart, & Cox, 1998). Moreover, students with high AS referred: more parental reinforcement of sick-role behaviour in response to their anxiety symptoms, more exposure to parental uncontrolled behaviour, and more parental sick role behaviour in response to parents' own anxiety symptoms compared to students with moderate and low level of AS (Watt et al., 1998).

The role of childhood emotional maltreatment on AS development was also examined by Scher and Stein (2003). Results showed that parental hostile, rejecting, and threatening behaviours predicted approximately 7% of the variance of AS. In addition, parental threatening behaviours predicted fears of social concern, accounting for 7.3% of variance, while parental hostile and rejecting behaviours predicted fears of losing control, accounting for 6.4% of variance (Scher & Stein, 2003). Thus, childhood emotional maltreatment seems a plausible candidate to be an environmental risk factor for AS.

Finally, some authors found that subjects with insecure attachment showed significantly higher AS score compared to securely attached individuals (Watt, McWilliams, & Campbell, 2005; Weems, Berman, Silverman, & Rodriguez, 2002).

3.1. Anxiety sensitivity and its role in psychiatric disorder

The association between AS and depression was studied for the first time by Otto and colleagues (1995). The authors examined the AS score in a group of depressed patients compared to healthy subjects; they found significantly elevated AS scores in the clinical group. They also examined, in a larger sample, the association between AS and the levels of somatic symptoms, dysfunctional attitudes, and depression and anxiety severity finding that AS score were strongly linked with dysfunctional attitudes and the severity of somatic symptoms among depressive patients, if compared to the control group, and that AS score decreased after treatment with antidepressant medication (fluoxetine) (Otto, Pollack, Fava, Uccello, & Rosenbaum, 1995). Progressively, it was suggested that AS may operate as a vulnerability factor for depression (Cox, Enns, Freeman, & Walker, 2001$_a$; Schmidt, Lerew, & Joiner, 1998; Tull & Gratz, 2008), and especially that a specific dimension of AS, fear of cognitive dyscontrol, was associated with heightened depressive symptoms (Taylor, Koch, Woody, & McLean, 1996; Zinbarg, Brown, Barlow, & Rapee, 2001).

Numerous study showed an association between the AS and the substance use disorders, especially for alcohol, hallucinogens (i.e., LSD), stimulants (i.e., cocaine, caffeine, and nicotine), opiates (i.e., heroin and morphine), and other drugs (i.e., inhalants, glue, and anabolic steroids). Patients with alcohol dependence are characterized by higher AS (DeMartini & Carey, 2011; Stewart, Samoluk, & MacDonald, 1999). In a longitudinal study, 404 subjects with no current psychiatric diagnoses were followed for 24 months to study the effects of AS on the development of alcohol use disorders (AUDs). Results showed that higher level of AS, and male gender, predicted

the development of AUD; specifically, the 6% of males and 2% of females with high AS developed AUDs, while 3% of males and 0% of females with low AS had AUDs, at 24-months follow-up (Schmidt, Buckner, & Keough, 2007).

According to a study conducted on a sample of 130 low-income racial/ethnic minorities, a significant indirect associations was found between AS and cannabis use problems, cannabis withdrawal symptoms, and use of cannabis to cope with stressful life events (Paulus, Manning, Hogan, & Zvolensky, 2016). In another study conducted on 49 undergraduates, it was observed that the mental incapacitation concerns, one of the factors of AS, was significantly associated with severity of cannabis-related problems (Buckner et al., 2011). Results also showed that individuals with higher craving and higher score on mental incapacitation and social concerns factor of AS had a higher probability to use cannabis (Buckner et al., 2011).

A great number of studies have been conducted on the association between anxiety and nicotine dependence and, recently, the focus has been shifted to the study of AS and its relation with cigarette smoking (Leyro, Zvolensky, Vujanovic, & Bernstein, 2008). It was found that AS was positively related with smoking expectancies for negative affect reduction as well as expectancies for negative consequences of smoking (Leyro et al., 2008). Smokers with high level of AS also perceived quitting as more difficult, compared to low AS smokers (Zvolensky et al., 2007); referred more intense nicotine withdrawal symptoms during smoking deprivation (Johnson, Stewart, Rosenfield, Steeves, & Zvolensky, 2012); and showed a higher probability of early relapse (Zvolensky, Stewart, Vujanovic, Gavric, & Steeves, 2009).

The relationship between AS and eating disorders has been rarely studied. According to a study that assessed AS and eating disorders symptoms on a clinical group (n=96) with a diagnosis of axis I psychiatric disorders (excluding psychotic- or bipolar-spectrum disorders) and 88 healthy undergraduates, AS was significantly related to bulimia scores, as measured by the Eating Disorder Inventory (EDI - Garner, Olmstead, & Polivy, 1983), even after controlling for depressive

symptomatology, trait anxiety, and impulsivity (Anestis, Holm-Denoma, Gordon, Schmidt, & Joiner, 2008). In the clinical sample, AS was also significantly correlated with “Drive for Thinness” of EDI subscale (Anestis et al., 2008).

Lilienfeld and Penna (2001) examined the relations between AS, as assessed by the ASI (Reiss et al., 1986), and measures of antisocial personality disorders, personality disorder features, and personality traits. In a sample of 104 university students, they observed that AS scores were not associated with antisocial personality disorders; conversely, a positive and significant association was observed with borderline and dependent personality disorder. Similarly, Gratz and colleagues (2008) found that borderline personality outpatients reported higher AS than non-personality disorder outpatients; and AS reliably distinguished between these two groups. In a recent study, Tucker, Lengel, Smith, Capron, Mullins-Sweatt, and Wingate (2016) found that the AS dimension of fear of cognitive dyscontrol mediated the relationship between maladaptive personality traits and suicidal ideation of a sample of undergraduates with borderline personality traits.

3.2. Anxiety sensitivity and anxiety disorders

A growing body of research indicated that AS amplifies fearful reactions, thus increasing the likelihood of onset of anxiety-related conditions (Olatunji & Wolitzky-Taylor, 2009). Actually, recent evidence has suggested that the association between the three lower order factors of AS and the development of specific anxiety disorders could be conceptualized in a hierarchical model (Olatunji & Wolitzky-Taylor, 2009; Zvolensky, & Schmidt, 2007).

A strong positive relation between AS (as a higher order construct) and panic was extensively demonstrated (Hayward, Killen, Kraemer, & Taylor, 2000; Schmidt et al., 1997), indicating that it is a specific risk factor for the development of panic (Olantunji & Wolitzky-Taylor, 2009). Indeed, in a popular study on 1172 cadets of the United States Air Force Academy (USAFA), Schmidt and colleagues (1997) analysed the predicted role of AS on the development of panic. The

authors evaluated the incoming 1st year cadets during their initial 5 weeks of training at the USAFA; this basic cadet training is characterized by extreme psychosocial stressors (e.g., isolation from friends and family, constant monitoring and evaluation of behaviour) as well as physical stressors (e.g., intense exercise, limited sleep). Results indicated that elevated ASI scores predicted clinically significant symptomatic distress and impairment, after controlling for trait anxiety and lifetime PAs. Almost 20% of cadets, scoring in the upper decile of the ASI, showed PAs during the 5-week follow-up relative to the only 6% for the remainder of the sample.

Regarding the fear of physical symptoms dimension, also called as AS-Physical concern, various results were obtained (Li & Zinbarg, 2007). In a longitudinal study (4-years) conducted on a non-clinical sample of adolescents, Hayward and colleagues (2000) found that only the AS-Physical concern dimension predicted the onset of PA symptoms. Conversely, Schmidt and colleagues (1999) observed that the fear of cognitive dyscontrol, also called as AS-Mental Concerns, was the best predictor of panic in young adults followed over a 5-week period. Olatunji and Wolitzky-Taylor (2009), summarizing the existing literature on this topic, stated that “the relation between AS and panic is almost entirely attributable to the fear of physical sensation dimension of AS” (p. 993).

Several studies found a close relationship between fear of publicly observable anxiety symptoms, also called as AS-Social concern and social anxiety disorder (McWilliams, Stewart, & MacPherson, 2000; Olatunji & Wolitzky-Taylor, 2009). Comparing the items pattern response of the ASI (Reiss et al., 1986) in subjects with PD and SAD, patients with social phobia had a significantly higher score on AS-Social concern items compared to PD patients (Hazen, Walker & Stein, 1994). In addition, evaluating 407 anxiety disorders patients regarding the latent structure of ASI, it was found that social phobic patients had a significantly higher score on AS-Social concern compared to PD and OCD patients (Naragon-Gainey, 2010; Zinbarg, Barlow, & Brown, 1997). Thus, the association between AS and SAD seemed to be characterized by anxiety-related sensations due to the probability of negative evaluation and not related to mental or physical concern (Olatunji & Wolitzky-Taylor, 2009).

Whereas AS-Physical concern and AS-Social concern have demonstrated to be respectively related to PD and SAD, evidence for the association of AS-Mental concern with a specific anxiety disorder are less clear (Olatunji & Wolitzky-Taylor, 2009). It was suggested that AS-Mental concern factor may be a non-specific measure of general distress. Researchers found that AS-Mental concern was moderately associated with GAD and depression (Rodriguez, Bruce, Pagano, Spencer, & Keller, 2004). However, AS-Mental concern seems to be also quite associated with OCD: evaluating the latent structure of ASI in a sample of OCD patients, Calamari and colleagues (2008) observed significantly higher loadings on AS-Mental concern and AS-Social concerns dimension compared to the AS-Physical concern.

Finally, a recent meta-analysis (Naragon-Gainey, 2010) of 117 studies and 792 effect sizes including normal and psychopathological population with internalizing disorders or symptoms, found that PD, GAD, and PTSD were strongly associated with AS, as a factor of higher order level. At the lower order level, PD was closely related to both AS-Physical and AS-Mental concern components of AS. Generalized anxiety disorders was largely associated to all three lower order components, although AS-Mental and AS-Social concern dimensions were the strongest. PTSD was most strongly related to the AS-Mental concern component of AS. SAD was definitively related to AS-Social concern, and agoraphobia to the AS-Physical concern. Obsessive-compulsive disorder and, particularly, specific phobia showed the weakest relation with AS (Naragon-Gainey, 2010).

3.3. Anxiety sensitivity and panic: data from the lab

Several empirical evidence have suggested that AS constitutes a specific risk factor for the development of panic (McNally, 2002). A body of studies, involving both PD patients and healthy individuals, demonstrated that AS may be a significant predictor of panic-like response to experimental laboratory challenge procedures (i.e., carbon dioxide inhalation, hyperventilation) (Eke & McNally, 1996).

Comparing the panic-like response of anxiety disorder patients and non-anxious controls to voluntary hyperventilation and continuos exposure to 5.5% CO_2, Rapee et al. (1992) found that the best pre-challenge predictors of panic reaction was the AS. Specifically, PD patients scoring high on AS-Physical concern subscale showed the greater anxiety response to each challenge. Furthermore, AS-Physical concern was the unique predictor of self-reported fear in a sample of healthy subjects who underwent the inhalation of 20% CO_2 enriched-air (Zvolensky, Feldner, Eifert, & Stewart, 2001).

Similarly Perna, Romani, Caldirola, Cucchi, and Bellodi (2003) found that AS was a good predictor of symptomatological reaction to 35% CO_2 challenge, but not of subjective anxiety as measured by the VAAS. They suggested that AS might be a dispositional vulnerability factor that amplifies somatic symptoms typical of PD.

Contrary to expectations, Forsyth, Palav, and Duff (1999) observed that university students with high, medium, and low AS did not differ in their autonomic/anxious response to 8 repeated 20-seconds inhalation of either 20% or 13% CO_2-enriched air. Similarly, although in a sample of PD patients, Koszycki and Bradwejn (2001) observed that the patients were not hyper-responsive to the 35% CO_2 challenge due to the high levels of AS. In addition, no association between AS and the severity of somatic symptoms induced by the challenge, or the severity of subjective anxiety, was observed (Koszycki & Bradwejn, 2001). Another interesting result has been recently obtained by Fluharty, Attwood, and Munafò (2016) who examined the association between anxiety proneness, and a range of subjective and physiological measures, and response to both 7.5% CO_2 and medical air (placebo) in a sample of healthy volunteers. They observed that anxiety proneness was associated with increased subjective and physiological responses to both CO_2 and placebo condition, but, surprisingly, the association was stronger for subjective anxiety when medical air was administered. The authors explained this result by assuming that the anticipatory anxiety associated with the challenge procedure was higher in subjects with high trait anxiety and high AS (Fluharty et al., 2016).

4. Perception of control

The concept of control, and its related constructs, has been largely studied in psychology (Gallagher, Bentley & Barlow, 2014). Depending on the theoretical framework, several definitions of control have been provided. According to Rotter (1966), we can distinguish between the external and the internal control. A reinforcement following a subject's behaviour, that is perceived as due to outside forces (such as fate, luck, or powerful others), is called external locus of control. Conversely, when the reinforcement is perceived as due to his own action, it is called internal locus of control (Rotter, 1966; Gallagher et al., 2014).

A different conceptualization was proposed by Bandura, as part of the self-efficacy theory (Bandura, 1977). He described the control as an estimation in which specific behaviour will produce certain outcome. Bandura's theory is related to the belief that a person can exercise control over life events (Bandura, 1977). Thus, perceived control, as the subject beliefs that desired outcomes can be produced, is distinct from the actual control that refers to the more objective conditions of control (Skinner, 1996).

When individuals lack in their belief to act effectively on life events, the probability to develop psychiatric disorders increase (Weems & Silverman, 2006). Particularly, several studies showed the etiological significance of perceived control in anxiety disorders (Gallagher et al., 2014). Referring to the Triple Vulnerability Model (see paragraph 1.3) (Barlow, 2002), the subjects with low perceived control present a generalized psychological vulnerability, which facilitates the development of neurotic temperament and, consequently, raises the proneness to develop an anxiety disorder. Causes for a decreased in perceived control may be sought in early experiences (such as parenting style characterized by overprotectiveness and intrusiveness) and uncontrollable events (i.g., trauma, abuse) (Chorpita & Barlow, 1998). A recent meta-analysis of 51 studies (with a total of 11218 participants) evaluated perceived emotional control and measure of anxiety showing a strong association between perception of control and trait anxiety. Specifically, the lowest the level of perceived control, the highest was anxiety as a trait. In addition, perceived control had moderate

association with PD with or without agoraphobia, OCD, PTSD, and social phobia, and a strong association with GAD (Gallagher et al., 2014).

4.1. Perception of control during the CO_2 challenge

Another set of studies investigated the effect of manipulation of context during panicogenic challenge procedure. One of the first studies examined the consequences of perception of control during continuos (15 minutes) 5.5% CO_2 inhalation and was conducted by Sanderson and colleagues (1989). They found that the sense of control during the challenge procedure could mitigate anxiety and panic-like response to the test. Specifically, PD patients who believed to be able to change the amount of carbon dioxide, signaled by an illumination of a light, showed lower number of PAs symptoms, rated the symptoms as less intense, reported lower subjective anxiety, lower number of catastrophic cognitions, and significantly less PAs compared to subjects who believed to not control (Sanderson et al., 1989).

Although on healthy subjects, Van Den Bergh and colleagues (1993) conducted a similar study and found that participants with high *versus* low trait anxiety (measured by the State Trait Anxiety Inventory - STAI) (Spielberger, Gorsuch, Lushene, Vagg, & Jacobs, 1983), who had control over the offset of a continuos exposure to 5.5% CO_2 challenge, did not differ from subjects with no control in term of panic-like response. This unexpected result was ascribed to some methodological limitations, first of all the fact that the STAI was a poor predictor of anxious responding to biological challenges in healthy people (Van den Bergh, Vandendriessche, De Broeck, & Van de Woestijne, 1993).

Thus, Zvolensky et al. (1999) performed a study on healthy subjects scoring high in AS. When randomized to the condition “lack of control”, individuals with high AS experienced more panic-like symptoms after repeated administrations of 20% CO_2 enriched-air. A lack of offset control produced greater self-reported anxiety compared to participants with illusion of control. The only exception was for heart rate, in which no significant differences were observed. In a subsequent

study, they found the same effect but only in women while no difference was observed in males (Zvolensky et al., 2001). Similarly, Telch and colleagues (1996) evaluating the effects of AS and perception of control on anxious responding to caffeine challenge, showed that individuals with high AS had more severe panic-like responses, compared to subjects with low AS.

Other groups of researchers focused their studies on the effect of instructional sets manipulation on panic-like response to a panicogenic challenge (Papp et al., 1995; Rapee, Mattick, & Murrell, 1986; Telch, Harrington, Smits, & Powers, 2011; Welkowitz et al., 1999; Zvolensky et al., 2001). To our knowledge, the fist study on this specific topic was conducted by Rapee and colleagues (1986) who compared the anxious responses to 50% CO_2 enriched-air in patients with PAs and in controls with specific phobia, randomly assigned to two different instructional set. The first instruction gave complete explanation concerning the consequences of gas inhalation; the second instruction did not give full explanations. Results showed that patients with PAs, who received no full explanations prior the inhalation, experienced more panic-like symptoms and higher catastrophic cognition compared to patients with PAs who received full explanation. No differences were observed between the two instructional sets for specific phobia subjects. The authors suggested that unexpected and surprising panic-like symptoms produced a higher misattribute and catastrophic tendency toward physical sensation in patients with PAs (Rapee et al., 1986). However, when Papp and colleagues (1995) attempted to replicate this study, they did not find statistically significant differences between the two instructional sets. It was hypothesized that methodological discrepancies (i.e., carbon dioxide concentration and administration technique) could account for their results (Papp et al., 1995).

Some years later, Telch and colleagues (2011) conducted an experimental study in which the joint effect of anxiety sensitivity and the set of instruction manipulation on panic-like response to the 35% CO_2 challenge was investigated (Telch et al., 2011). They recruited 700 psychology undergraduates who underwent a screening assessment with the ASI (Reiss et al., 1986). According to the ASI scores, participants were split in two groups: those with a high AS (one Standard

Deviation [SD] or more above the mean), and those with low AS (one SD or more under the mean). Students having a score with only one SD above the mean or with only one SD under the mean, with lifetime or current PAs or PD, with medical illness, or assuming psychotropic medication were excluded.

The enrolled subjects were assessed at baseline; they completed self-reported psychological questionnaires, including the STAI, the Beck Anxiety Inventory (BAI; Beck, Epstein, Brown, & Steer, 1988), the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), and the Anxiety Questionnaire (AQ), a 15-item instrument, to evaluate the presence of PAs or PD according to the DSM-III (APA, 1980). Then, they took part at the test-phase. The measure of vital capacity of breath and heart rate were evaluated. Participants were invited to sit in a comfort chair and relax for some minutes. The experimenter read the instructions relative to the two gas inhalation (CO_2-enriched air and of room air); the order of gas administration was counter-balanced. To blind participants' expectations concerning the effects of the gas, the set instruction was manipulated and assigned in a randomized order. In one case the instruction provided correct information regarding the effect of CO_2 inhalation (Arousal Expectancies - EA); whereas, in the manipulated condition the instruction created the expectation that CO_2 might be relaxing (Relaxation Expectancies - ER). Consequently, four groups were formed: 1) High level of AS and EA (HAS-EA); 2) High level of AS and ER (HAS-ER); 3) Low level of AS and EA (LAS-EA); 4) Low level of AS and ER (LAS-ER). Thereafter, the four groups underwent the standardized 35% CO_2 challenge procedure (Verburg et al., 2001). Immediately before and immediately after each inhalation (35% CO_2 challenge and room air), the subjects were asked to fill in the Acute Panic Inventory (API; Liebowitz et al., 1984) and the Subjective Units of Distress Scale (SUDS; Wolpe, 1969) as measure of panic response to the challenge. Telch and colleagues found that HAS subjects had higher anxiety responses, compared to subjects with LAS on the BAI ($F(1, 75) = 42.67$, $p < .0001$), the BDI ($F(1, 74) = 37.19$, $p < .0001$), the STAI-1 ($F(1, 75) = 30.51$, $p < .0001$), and the STAI-2 ($F(1, 75) = 51.10$, $p < .0001$). Furthermore, the HAS-ER group showed higher anxiety

response compared to HAS-EA group on API total change score (76% *versus* 56%), on self reported panic (62% *versus* 33%), and on DSM-IV panic criteria (57% *versus* 22%) in response to the 35% CO_2 challenge. The authors hypothesized that the emotional responses to the CO_2 were more intense, compared to the room air and to subjects who received the correct instruction (EA), due to the fact that the reaction toward CO_2 was unexpected and because they experienced a strong disconfirmation of their expectations.

The data from Telch and colleagues (2011) confirmed the predictive role of AS on physiological and psychological responses to the CO_2 challenge. However, the most interestingly results were related to the influence of challenge instruction on the subjective anxiety responses. Study limitations identified by the authors were:

- the selection of participants (i.e., introductory psychology students, who participated for partial class credit at the University of Texas) with the highest and lowest level of AS might have overestimated the effect sizes;
- the only physiological measure evaluated was heart rate;
- exclusion criteria referred to current or lifetime PAs or PD diagnosis rather than to all axis I psychiatric disorder diagnosis;
- caffeine or alcohol intake were not not assessed although they can affect the physiological response (Charney et al., 1985).

4.2. Aims of the study

The purpose of the present research was to replicate Telch and colleagues' (2011) study to overcome some methodological limitations. The main experimental changes compared to the original study are:

1. participants were screened using the Structure Clinical Interview for DSM-IV - Patient Version (SCID-I-P) (First, Spitzer, Gibbon, & Williams, 2002a) to exclude current or lifetime Axis I psychiatric disorder(s) which might compromise the response to the test (Fluharty et al., 2016).

2. Participants were not pre-selected according to the level of AS, which was evaluated after the screening session. The aim was to avoid sampling errors, since subjects with the highest and lowest score on ASI could undermine the representativeness of the sample and the results extension to the general population.
3. The last version of the Anxiety Sensitivity Index -3 (ASI-3; Taylor et al., 2007), recently validated also in Italian (Petrocchi, Tenore, Couyoundjian, & Gragnani, 2015), was used to assess anxiety sensitivity. Compared to the first version of the ASI (Peterson & Reiss, 1992), that it was used by Telch and colleagues (2011), the ASI-3 has shown better psychometric properties, such as a more stable factor structure and greater construct validity.
4. The Somatosensory Amplification Scale (SSAS; Barsky, Wyshak, & Klerman, 1990) and the Illness Attitudes Scale (IAS; Kellner, 1987) were added at baseline to assess if unpleasant physical sensations were interpreted as intense, harmful, or associated with physical illness. Indeed, high SSAS or IAS might affect or increase the anxiety response following the inhalation of CO_2 (Cosci, Ibrahim, Nannini, & Schruers, 2015).
5. Participants were assessed at baseline for caffeine and alcohol daily consumption, since caffeine or alcohol may affect the physiological response (i.e., blood pressure and heart rate) to the test (Charney et al., 1985).
6. The instruction (Expected Arousal or Expected Relaxation) was administered before CO_2 and room air inhalation, rather than at the only beginning of the test-phase, to be sure that each subject was aware of its content.
7. The subjects underwent a double inhalation CO_2 challenge rather than a single inhalation. Indeed, evidence suggested that double inhalation elicits a greater response in healthy subjects (Nardi et al., 2006; Rassovsky & Kushner, 2003).
8. VAAS, VAS-F, and VAS-D were administered to measure subjective anxiety, fear, and discomfort, respectively, as experienced by the subject after the both inhalations, instead of the

Subjective Units of Distress Scale (SUDS) since VAAS, VAS-F, and VAS-D are specifically used to measure panic-like symptoms according to the 35% CO_2 challenge standardized procedure (Verburg et al., 2001).

9. The Panic Symptom List (PSL) was used instead of the Acute Panic Inventory (API; Liebowitz et al., 1984) since PSL is specifically used to measure panic-like symptoms according to the 35% CO_2 challenge standardized procedure (Verburg et al., 2001).
10. Immediately before and immediately after each inhalation, the blood pressure and heart rate were measured in order to evaluate the physiological response to the challenge and according to the 35% CO_2 standard procedure.

The general aim of the study was to verify if AS and the manipulation of expectations (i.e., two different set of instructions) might affect the psychological and physiological responses to the 35% CO_2 inhalation. Specifically, healthy subjects with high or low AS and with no history of PD or unexpected PAs were enrolled. Each participant underwent a double inhalation of 35% CO_2-enriched air and regular room air, administered in a counter-balanced order. To manipulate participants' expectations on the contents and the effects of the gas mixture (35% CO_2-enriched air *versus* room air), two different challenge instructions were provided: in one case the instruction informed that the CO_2 mixture might have physically arousing effects (expected arousal); in the other case the challenge instruction informed that the CO_2 mixture might have relaxing effect (unexpected arousal).

The expected results are: high AS subjects have a more severe panic-like response to the CO_2 challenge compared to subjects with low levels of AS; high AS subject who received relaxation instruction have a more severe panic-like response to the test compared to high AS subject who received arousal instruction.

Chapter 2. Methods

1. Sample

Ninety-six healthy subjects, 40 males and 56 females, recruited from the Florence general population were contacted through notices and posters placed in academic and public places. Participants with current or lifetime history of Axis I psychiatric disorders, evaluated through the SCID-I (First et al., 2002a) were excluded. Subjects were also excluded in presence of current or lifetime cardiovascular disorders (e.g., infarct, angina pectoris, cardiac arrhythmia); lung disease (including asthma); hypertension (diastolic blood pressure > 120 mmHg; systolic blood pressure > 180 mmHg), history of seizures or coma; gastrointestinal disorders (i.e., ulcers); treatment with psychotropic drugs (i.e., antidepressants, benzodiazepines, mood stabilizers, neuroleptics); current treatment with α2- and β-blockers; current pregnancy and/or lactation; inability to give informed consent. These exclusion criteria were investigated through an additional set of screening questions filled before the administration of the SCID-I.

According to these criteria, 28 subjects were excluded. Specifically, 8 subjects had current or lifetime PAs or PD diagnosis; 4 subjects had current Substance Use Dependence or Abuse diagnosis; 4 subjects had current or lifetime Major Depression diagnosis; 2 subjects had asthma; 2 subjects were under psychotropic drugs; 2 subjects had organic disease; 1 subject had current Generalized Anxiety diagnosis; 1 subject dropped out; 1 subject was accidentally informed about the CO_2 effect; and 3 subjects did not correctly understand the instruction read by the researcher (i.e., they received the EA instruction, but they referred to understand ER instruction). Therefore, the final sample was composed by 68 healthy subjects, 28 males and 40 females, aged between 18 and 65 years.

2. Study design

A 2x2x2 mixed model design was used to test the single and joint effects of AS (low *versus* high), the instructional set (expected arousal *versus* expected relaxation), and inhalation mixture (35% CO_2 *versus* room air). The level of AS and the instructional set were used as between-group factors. The inhalation mixture was included in the model as a within-subjects factor.

The normative data of the Italian sample were used to stratify participants for the level of anxiety sensitivity, (Petrocchi et al., 2015). Males with an average ASI-3 score ≤ 11.21 (SD=8.68), and females with an average ASI-3 scores ≤ 12.93 (SD= 9.55) were assigned to the low AS group (LAS). Males with an average ASI-3 score ≥ 11.21 (8.68) and females with an average ASI-3 score ≥ 12.93 (9.55) were assigned to the high AS group (HSA).

Subjects were matched for sex, age, level of AS (high *versus* low and with at least a difference of one SD), and each couple of participants was thereafter randomly assigned to the expected arousal (EA) set of instruction or to the expected relaxation (ER) set of instruction. Thus, four groups were obtained: 1. low level of anxiety sensitivity and expected arousal (LAS-EA); 2. low level of anxiety sensitivity and expected relaxation (LAS-ER); 3. high level of anxiety sensitivity and expected arousal (HAS-EA); 4. high level of anxiety sensitivity and expected relaxation (HAS-ER).

3. Instruments

3.1. Structured Clinical Interview for DSM-IV – Patient Version (SCID-I-P)

The SCID is a semi-structured clinical interview developed by First and colleagues (2002a) and able to formulate the major DSM-IV Axis I and Axis II diagnoses.

The SCID is divided into separate modules (8 or 9 sections) corresponding to categories of DSM-IV diagnoses. Each section begins with an entry question and, if the criterion is not satisfied, allows the interviewer to skip rest of the module and continue with the next one. For all diagnostic categories, symptoms are coded as present (coded with number 3), sub-threshold (coded with number 2), or absent (coded with number 1). Each module is independent and can be used separately.

For adults, two main versions of Axis I clinical disorders, and one version of Axis II personality disorders are available. The SCID-I-P (Patient Edition) is developed for use with individuals who are identified as psychiatric patients. The SCID-I-NP (Non-patient Edition) is designed for use in studies in which the subjects are not identified as psychiatric patients. The only difference between the two editions is in the “Overview section”, in which questions to investigate about a history of psychopathology are not available in the SCID-I-NP (First, Spitzer, Gibbon, & Williams, 2002b).

The SCID should be administered by a clinician or trained interviewers who have extensive clinical experience with the particular study population. The time of administration for the SCID-I can range from 15 minutes (i.e., subjects without psychiatric history) up to several hours (i.e., subjects with extensive psychiatric comorbidity). Usually, time of administration for psychiatric patients likely average around 90 minutes, whereas for non-psychiatric patients it is about one hour. Administration time depends on subjects’ psychiatric history and their ability to answer questions clearly and concisely.

The SCID-I-P (First et al., 2002a) has shown an excellent inter-rater reliability, as assessed in a sample of 151 participants (Lobbestael, Leurgans, & Arntz, 2011). The kappa values for Axis I disorders varied from 0.61 to 0.83.

3.2. Anxiety Sensitivity Index 3 (ASI-3)

The first version of the ASI was developed by Peterson and Reiss (1992) and was composed of 16-item, evaluating the fear of bodily and related sensations. Despite its good psychometric properties (Peterson & Plehn, 1999), inconsistent results were obtained concerning the factor structure of the ASI (Blais, Otto, Zucker, McNally, Schmidt, Fava, & Pollack, 2001; Peterson & Heilbronner, 1987). Indeed, the AS was initially conceptualized as an unidimensional construct but, together with an higher-order factor (the general AS), three lower-order factors were identified according to numerous factorial studies (Taylor, 1999): the Physical Concerns, which refers to the fear of somatic sensations; the Social Concerns, which refers to the fear of publicly observable anxiety symptoms that may cause social rejection; and the Cognitive Concerns, which refers to the fear of cognitive or psychological dyscontrol. Thus, the instrument was composed of 8 items related to the Physical Concerns factor (i.e., “It scares me when my heart beats rapidly”), 4 items related to the Social Concerns factor (i.e., “It is important to me not to appear nervous”), and 4 items related to the Cognitive Concerns factor (i.e., “When I am nervous, I worry that I am mentally ill”).
The unequal item distribution and the weak content validity of the Social Concern and the Cognitive Concern factors led researchers to develop a revised form of the ASI (ASI-R; Taylor & Cox, 1998). The ASI-R was composed of 36 items and included 4 factors: the fear of respiratory symptoms, the fear of publicly observable anxiety reactions, the fear of cardiovascular symptoms, and the fear of cognitive dyscontrol. The ASI-R showed unstable and not fully satisfying factor structures (Armstrong, Khawaja, & Oei, 2006), suggesting the need of a further version: the ASI-3 (Taylor et al., 2007).

The ASI-3 consists of 18 items and evaluates the Physical, Social, and Cognitive Concerns factors, as conceptualized in the original version of the instrument. Each factor is composed of 6 items (Taylor et al., 2007). The response format is on a 5-point Likert scale ranging from 0 (“not at all”) to 4 (“very much”). Scores from a minimum of 0 to a maximum of 72 are calculated summing the item scores; the higher the score, the higher is the level of anxiety sensitivity (Taylor et al., 2007). Several studies have been conducted to study the psychometric properties of ASI-3 (Osman, Gutierrez, Smith, Fang, Lozano, & Devine, 2010; Taylor et al., 2007; Wheaton, Deacon, McGrath, Berman, & Abramowitz, 2012). The instrument showed good internal consistency, with alphas coefficient ranging from 0.79 (Canadian non clinical sample) to 0.86 (Canadian clinical sample) for Physical concern factor, from 0.79 (French sample) to 0.91 (Canadian clinical sample) for Cognitive concern factor, and from 0.73 (Mexican sample) to 0.86 (Canadian clinical sample) for Social Concern factor (Taylor et al., 2007). In regard to ASI-3 total score, Wheaton and colleagues (2012) found an excellent reliability (α= 0.93). ASI-3 also obtained a good convergent, discriminant, and criterion-related validity (Taylor et al., 2007).

Concerning the Italian version of the ASI-3, two main studies were conducted (Ghisi, Bottesi, Altoè, Razzetti, Melli, & Sica, 2016; Petrocchi et al., 2015). Results from the Confirmatory Factory Analysis (CFA) showed that the original three-factor hierarchical structure (Taylor et al., 2007) provided the best fit indices (Petrocchi et al., 2015), although Ghisi and colleagues (2016) found that the best factor solution was a bifactor model. ASI-3 showed a high temporal stability (1-months test retest, r = 0.76) (Ghisi et al., 2016), adequate convergent and discriminant validity (Ghisi et al., 2016; Petrocchi et al., 2015). The reliability for ASI-3 total score was good, ranging from 0.79 (Ghisi et al., 2016) to 0.90 (Petrocchi et al., 2015) in non-clinical samples. In an Italian clinical sample (n=154), the alpha coefficient was found excellent (α= 0.93) (Petrocchi et al., 2015).

3.3. Somatosensory Amplification Scale (SSAS)

The SSAS (Barsky et al., 1990) is a self-report instrument that evaluates the somatosensory amplification: the tendency to perceive the unpleasant physical sensations (but not pathological) as intense, harmful, and disturbing. The SSAS can be used to assess somatic amplification both in healthy subjects and in patients treated for psychosomatic diseases (i.e., irritable bowel syndrome, chronic pain), psychiatric disorders (i.e., somatoform disorders, anxiety disorders, depressive disorders), or medical disorders (i.e., infectious disease, heart disease).

The scale consists of 10 items, with a response format on a 5-point Likert scale, ranging from 1 (never) to 5 (always); it can be filled in by the subjects quickly (less than 10 minutes). The items cover a range of unpleasant physical sensations, most of which are not considered harmful (e.g., "I hate the too hot or too cold", "I cannot stand the smoke", "stand a little pain").

The SSAS total score is obtained by summing the score of each item: it ranges from a minimum of 10 to a maximum of 50; the higher the score, the more severe is the level of somatosensory amplification. The SSAS showed a good internal consistency (α=0.82) and a satisfactory test-retest reliability (Person's correlation ranging from 0.79 to 0.87). Evidence on convergent and concurrent validity of the SSAS were conflicting (Bridou & Aguerre, 2013).

3.4. Illness Attitude Scale (IAS)

The IAS, developed by Kellner (1986; 1987), is a self-report questionnaire assessing attitudes, fears, and beliefs associated with hypochondriasis and abnormal illness behaviour.

The instrument consists of 27 items, distributed on 9 subscales (3 items each): 1) Worry about Illness (WI; general worry about having a serious illness), 2) Concern about Pain (CP; concerns that physical pain experiences may be a sign of an underlying disease), 3) Health Habits (HH; avoidance of harmful behaviours), 4) Hypochondriacal Beliefs (HB; belief to be affected by a disease), 5) Thanatophobia (TH; fear of death), 6) Disease Phobia (DP; worries about having specific disease),

7) Bodily Preoccupations (BP; a sensitivity to bodily sensations which may be indicative of illness), 8) Treatment Experiences (TE; how frequently a person has sought medical treatments), and 9) Effects of Symptoms (ES; the extent to which bodily symptoms interfere with general functioning). For 24 items the response format is on a 5-point Likert scale ranging from 0 (“no”) to 4 (“most of the time”), the remaining 3 items are open-ended questions and do not contribute to the scores. According to the instructions, 3 versions are available: the state version, which is limited to the last month; the trait version, which is focused on how the subjects usually feel; and the standard version, without time focus.

The IAS total score is calculated by summing each item: it ranges from 0 to 108 (the highest score for each subscale is 12). IAS total scores are indicative of severity of abnormal illness behaviour.

Mixed results concern the factorial structure of the IAS were obtained, although the IAS was not develop according to a factorial analysis, but rather via a priori clinical selection of the items (Kellner, 1986; 1987). Subsequent factorial studies found both 2-factors solution, related to health anxiety and illness behaviour (Crössmann & Pauli, 2006; Speckens, Spinhoven, Sloekers, Bolk, & van Hemert, 1996; Wise & Sheridan, 2001), or a 4-factor solution associated with the fear of illness, the effects of symptoms on daily life, the disease phobia and conviction, and the avoidance of harmful health habits (Ferguson & Daniel, 1995; Hadjistavropoulos, Frombach, & Asmundson, 1999; Sirri, Grandi, & Fava, 2008). The IAS internal consistency is quite acceptable, although some subscales are below Cronbach’s alpha of 0.70 (Sirri et al., 2008). The instrument showed a good test-retest reliability, was able to discriminate between patients with hypochondriasis and controls (discriminant validity), and was positively correlated with other hypochondriasis-related measures, such as the Multidimensional Inventory of Hypochondriacal Traits and the SSAS (convergent validity) (Sirri et al., 2008).

3.5. Beck Anxiety Inventory (BAI)

The BAI is a 21-item self-report questionnaire assessing the severity of anxious symptoms (Beck et al., 1988). The instrument was designed to discriminate, thus minimizing, the overlap between anxiety and depression (Beck et al., 1988). The item response format, referred to the past week, is on a 4-point Likert scale, ranging from 0 (“not at all”) to 3 (“Severely-I could barely stand it”). The BAI total score is obtained summarizing each item, ranging from a minimum score of 0 to a maximum of 63. As suggested by Beck and Steer (1993), scores between 0 and 7 are indicative of “minimal” anxiety severity, between 8 and 15 indicate “mild” anxiety, between 16 and 25 “moderate”, and between 26 and 63 indicate “severe” anxiety. The BAI can be administered to adolescent, adults, and elderly with anxiety or affective disorders, and it requires about 5-10 minutes to be completed.

Several studies investigated its psychometric properties (Beck et al., 1988; Creamer, Foran & Bell, 1995; Fydrich, Dowdall, & Chambless, 1992; Osman, Kopper, Barrios, Osman, & Wade, 1997). Internal consistency (Cronbach’s alpha) was found high (α=0.94), the item-total correlations ranged between 0.30 and 0.71, and the test-retest correlation (1-week) was 0.75, thus suggesting a good reliability (Beck et al., 1988). Pearson’s correlation, with the STAI-trait and the STAI-state, were respectively r=0.58 and r=0.47, suggesting a good convergent validity (Fydrich et al., 1992). Moderate correlation were also observed with other instruments assessing anxiety, such as the Hamilton Anxiety Rating Scale (HARS; Hamilton, 1959) and the Cognition Check List (CCL-A; Beck, Brown, Steer, Eidelson, & Riskind, 1987). Discriminant validity revealed a high correlation (r=0.48) with the BDI, whereas the correlation was lower with the Hamilton Depression Rating Scale (r=0.25) (HDRS; Hamilton, 1960). Studies on the factorial structure of the BAI found a 2-factor (i.e., somatic symptoms dimension and subjective anxiety/panic dimension) (Beck et al., 1988; Creamer et al., 1995; Hewitt & Norton, 1993) or a 4-factor solution (i.e., neurophysiological symptoms, subjective anxiety, panic, autonomic aspects of anxiety dimensions) (Enns, Cox, Parker,

& Guertin, 1998; Osman et al., 1997), and the latter provided the best fit when confirmatory factor analysis was run (Osman, Hoffman, Barrios, Kopper, Breitenstein, & Hahn, 2002; Wetherell & Areán, 1997).

The Italian version of the BAI was validated in a non-clinical sample of undergraduates, showed good psychometric properties and a 4-factor solution (Coradeschi, Sica, Ghisi, Sanavio, Novara, Dorz, & Chiri, 2007).

3.6. Beck Depression Inventory (BDI)

The BDI is a widely used self-report questionnaire assessing depressive symptomatology (Beck et al., 1961). It is composed of 21 items; the response format is on a 4-point Likert scale, based on the severity of the content of the alternative statements (from 0 “absent” to 3 “severe”). For the last and revised version of the BDI (also called as BDI-II; Beck, Steer, & Brown, 1996), 4 items were dropped and replaced with items related to agitation, worthlessness, concentration difficulty, and loss of energy. The BDI has been developed in different forms, including a computerized forms and the 13-item short form (Beck, Rial, & Rickets, 1974).

The total score, ranging from 0 to 63, is calculated by summing the score obtained for each item. The cut-off varies based on the severity of the depression: a total score of 10 or less indicates absence of depression or minimal depression, a total score from 10 to 18 refers to mild or moderate depression, from 19 to 29 refers to moderate or severe depression, and from 30 to 63 indicates severe depression (Beck & Beamesderfer, 1974). The BDI takes approximately 10 minutes to be filled in and can be administered to adults and adolescent aged 13 years or older.

According to a seminal review of the literature (Beck, Steer, & Garbin, 1988), including the major research studies on the psychometric properties of the Beck Depression Inventory, BDI had a high internal consistency for both psychiatric populations (alpha coefficients ranging from 0.76 to 0.95; mean $\alpha = 0.86$), and non-clinical samples (alpha coefficients ranging from 0.73 to 0.92; mean

α = 0.81). Moreover, BDI showed a good test-retest reliability for psychiatric (ranging from r=0.48 to r=0.86) and non-psychiatric samples (ranging from r=0.60 to r=0.83). The BDI had a good convergent validity, as measured by the correlation with the HDRS (r = 0.73), and the Zung Self Rating Scale for Depression (Zung, 1965) (r= 0.76). Concerning the discriminant validity, the BDI proved to be able in differentiating healthy subjects and psychiatric patients (Beck et al., 1988). Studies on the factorial structure produced mixed results: the number of factors ranged from 3 to 7, depending on the extraction procedure used (Beck et al., 1988). The Italian version of the BDI was validated by Scilligo (1983), whereas the BDI-II was validated by Ghisi and colleagues (2006). The internal consistency was good (Cronbach's alpha = 0.80) and the item-total correlations ranged between 0.30 and 0.46. One-month test-retest correlation, on a sub-sample of 60 students, was acceptable (*r* = .76). The Italian version of the BDI showed a good convergent validity (*r* = 0.77) with the Questionnaire of Depression (QD) of the Cognitive Behavioural Assessment (CBA; Sanavio, Bertolotti, Michielin, Vidotto, & Zotti, 1986).

3.7. State-Trait Anxiety Inventory (STAI)

The STAI (Spielberger, Gorsuch, & Lushene, 1970) is a brief and reliable self-report scale composed of 40-item: 20 items assess the State Anxiety (S-Anxiety) and 20 items the Trait Anxiety (T-Anxiety). S-Anxiety subscale, whose items measure how a person feels at the testing time, evaluates the intensity of anxiety as an emotional state. T-Anxiety subscale, which measures how the subject feels generally, is defined as a relatively stable anxiety proneness. Items response format is on a 4-point Likert scale ranging from 1 (“almost never”) to 4 (“almost always”). The S-Anxiety and T-Anxiety subscale scores, calculated by adding the score of the items pertaining to each subscale, range from 20 to 80 with the higher score indicating greater anxiety.

The first version of the STAI (Form X) was developed in 1970 (Spielberg et al., 1970), but in order to provide a valid instrument for differentiating between anxious patients and depressive patients in

clinical diagnosis, a major revision of the inventory (STAI, Form Y) was made in 1983 (Spielberg et al., 1983). Specifically, items with depressive content, evaluated according to a factorial analyses, were eliminated and replaced, conferring to the STAI-Y better psychometric properties.

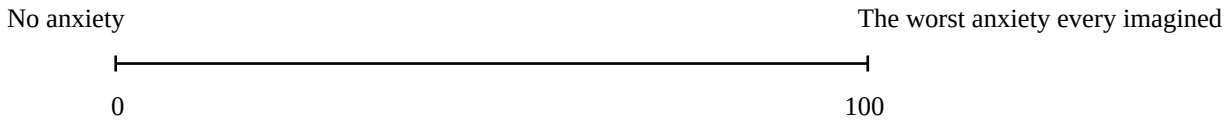
Several studies showed a good reliability of the STAI-Y (for a review see: Barnes, Harp, & Jung, 2002). Internal consistency for the S-Anxiety subscale ranged from α=0.90 or higher, with a median coefficient of α=0.93. The alpha coefficients for the T-Anxiety subscale were also excellent, with a median coefficient of α=0.90. As expected, test-retest stability for the T-Anxiety subscale was very high ranging from *r*=0.73 to *r*=0.86, whereas for the S-Anxiety subscale was lower, with a median Pearson's coefficient of 0.33. The STAI-Y showed also a high correlation with the Anxiety Scale Questionnaire (r=0.73) (ASQ; Cattell & Scheier, 1963) and the Manifest Anxiety Scale (r=0.85) (MAS; Taylor, 1953), indicating a high degree of convergent validity (Spielberger & Sydeman, 1994). The Italian version of the STAI-Y was provided by Pedrabissi and Santinello (1989) and showed a good and comparable psychometric properties to the original version.

3.8. Visual Analogue Scale of Anxiety (VAAS)

The Visual Analogue Scale (VAS) is a common single-item instrument, self-administered, which measures a variety of subjective phenomena (Patrician, 2004; Wewers & Lowe, 1990).
The VAS is a straight line, 100 millimeters long, anchored at both ends; typically, the anchors are bipolar antonyms.
The VAAS (see Figure 1) assesses subjective anxiety on a range from "no anxiety" (0 mm) to "the worst anxiety ever imagined" (100 mm). To respond, subjects place a single point on the line at or between the anchors which best represent their current level of anxiety. The VAAS score is obtained measuring the distance (in millimeters) from "0" anchor to the response point (Wewers & Lowe, 1990).

The VAAS is a simple scale, quick to be filled in, and useful for repeated measurements. It was used in many fields, especially to evaluate the perioperative and postoperative anxiety in children and adults (Bringuier, Dadure, Raux, Dubois, Picot, & Capdevila, 2009). The VAAS was also used to measure the subjective anxiety response toward panicogenic challenge procedures (Cosci et al., 2015; Knuts et al., 2010; Masdrakis, Markianos, Vaidakis, Papageorgiou, & Pehlivanidis, 2009).

Figure 1. The Visual Analogue Scale of Anxiety (VAAS)

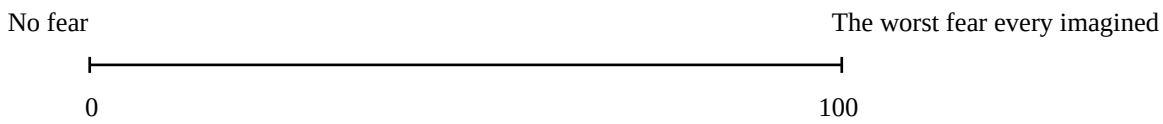


3.9. Visual Analogue Scale of Fear (VAS-F)

The VAS-F is a self-administered analogue scale assessing the level of subjective fear, through a straight line that ranges from 0 mm (“no fear”) to 100 mm (“the worst fear never imagined”) (see Figure 2). The VAS-F is used to assess subjective fear in response to laboratory challenge procedure, such as CO_2 inhalation (Cosci et al., 2015; Esquivel, Dandachi, Knuts, Gossens, Griez, & Schruers, 2012).

In a modified version, the VAS-F has been also used in the medical area to evaluate the fear of falling in the elderly (Scheffer, Schuurmans, van Dijk, van der Hooft, & de Rooij, 2010), and the fear of anesthesia and surgical interventions (Kindler, Harms, Amsler, Ihde-Scholl, & Scheidegger, 2000).

Figure 2. The Visual Analogue Scale of Fear (VAS-F)

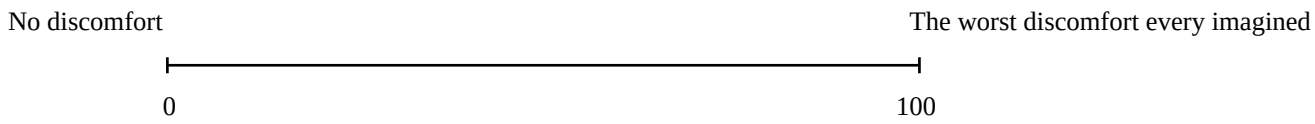


3.10. Visual Analogue Scale of Discomfort (VAS-D)

The VAS-D is a self-administered analogue scale assessing the level of perceived discomfort as experienced by the subject; the discomfort is measured on an horizontal line ranging from 0 mm (“no discomfort) to 100 mm (“the worst discomfort ever imagined”) (see Figure 3).

The VAS-D is used to assess the subjective level of distress after the CO_2 challenge procedure in some recent studies (Cosci et al., 2015; Esquivel et al., 2012).

Figure 3. The Visual Analogue Scale of Discomfort (VAS-D)



3.11. Panic Symptom List (PSL)

The PSL is a self-report questionnaire, composed by a list of DSM-IV TR (APA, 2000) panic symptoms (Schruers, Klaassen, Pols, Overbeek, Deutz, & Griez, 2000). The response format is on a 5-point Likert scale ranging from 0 (“not at all”) to 4 (“extreme”). The total score, calculated by adding the score of each item, ranges from 0 to 52; the higher the score, the most severe is the panic symptomatology. The PSL is used to evaluate subjective response to the induction of panic via laboratory challenge procedures (Cosci et al., 2015; Schruers et al., 2000).

4. Procedures

The study was carried out at the Laboratory of Health Psychology, Department of Health Sciences, University of Florence. The procedure included two phases: the screening assessment and the test day (see Figure 4).

During the screening assessment, the informed written consent was collected. Then, the subjects were assessed via the SCID-I (First et al., 2002_a) to investigate the presence of Axis I psychiatric disorders; the SCID-I was administered by a trained psychologist (GB). Participants also answered to an additional set of screening questions to exclude the presence of medical pathologies contraindicated for the CO_2 administration. Due to the relationship between cigarette smoke and panic (Cosci et al., 2010; Knuts et al., 2010), the smoking status and the average number of cigarettes smoked were asked. If eligible, the subjects were invited to complete the following self-report questionnaires: the ASI-3 (Taylor et al., 2007), the SSAS (Barsky et al., 1990), the IAS (Kellner, 1986), the BAI (Beck et al.,1988), the BDI (Beck et al., 1961), and the STAI (Spielberger et al., 1983). Thereafter, psychophysiological parameters, such as blood pressure and heart rate, were measured. To avoid physiological biases, the subjects were informed not to consume alcohol or drugs until the start of the experimental phase.

On the basis of the ASI-3 scores as well as the random allocation of the instructions (Expected Arousal *versus* Expected Relaxation), subjects were assigned to 4 different groups (see "Study Design" paragraph); they were also matched for age, sex, and level of AS. The subjects of each couple received the same instruction and the same order of gas mixture (35% CO_2 *versus* room air).

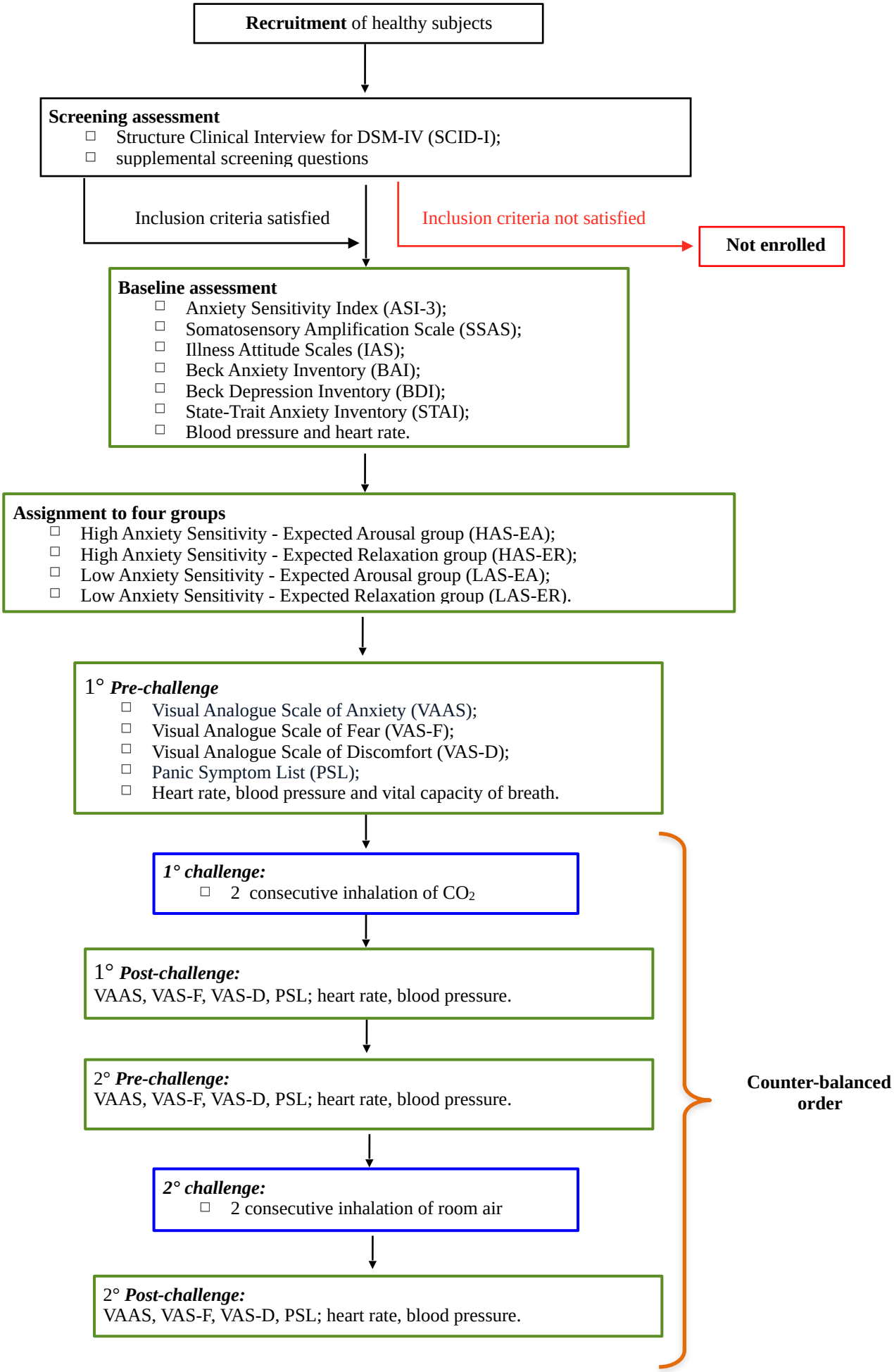
At the test day, information on daily consumption of caffeinated products assumed between the awakening and the beginning of the test was collected, since caffeine may affect the physiological response (i.e., blood pressure and heart rate) to the test. Thereafter, participants were invited to fill in the following rating scales (we called this assessment "first pre-test"): VAAS, VAS-F, VAS-D, and PSL; blood pressure and heart rate were also measured. Thereafter, the subjects

underwent the challenge procedure which started measuring the respiratory vital capacity (i.e., the maximum amount of air a person can expel from the lungs after a maximum inhalation), via the Wright respirometer Mark™ connected to a self-administration mask. Participants were instructed to exhale as deeply as possible, wear the mask, and inhale as much air as possible from the mouth. They had to hold the breath for 4 seconds, and finally exhale. Then, participants were informed to sit quietly and relax for 4 minutes. The researcher re-entered in the room and read the assigned instructions (see next paragraph). Thus, participants underwent a double inhalation of the first gas mixture (35% CO_2 or room air), remaining unaware of the order of gas administration (the 35% CO_2 and room air administration was counter-balanced). Immediately after the inhalation, subjects filled in the VAAS, the VAS-F, the VAS-D, and the PSL; a research assistant measured the blood pressure and the heart rate (we called this assessment “first post-test”).

Ten minutes later, participants were invited to fill in again the VAAS, the VAS-F, the VAS-D, and the PSL, their physiological parameters were also measured (we called this phase “second pre-test”). A research assistant read, for a second time, the assigned instruction (Expected Arousal or Expected Relaxation). Then, participants underwent a double inhalation of the second gas mixture (35% CO_2 or room air). Immediately after the inhalation, they were asked to fill in the VAAS, the VAS-F, the VAS-D, and the PSL, blood pressure and the heart rate were measured (we called this phase “second post-test”). To be considered valid, the gas mixture inhalations had to be equal to the 80% of the subject’s vital capacity of breath.

At the end of the second post-test, participants completed a short questionnaire to assess the integrity of the instructional set manipulation.

Figure 4. Schematic overview of the whole procedure



4.1. Instructions manipulations

Participants assigned to the Expected Arousal condition received the following instructions:

- “this study investigates the effects of carbon dioxide inhalation on mood. You will be taking a double vital capacity breath containing either 35% carbon dioxide and 65% oxygen or normal room air. Breathing the carbon dioxide mixture may result in various physical feelings of arousal such as rapid breathing, heart rate acceleration, sweating, and dizziness or lightheadedness. Breathing in the room air will not result in any different physical feelings besides those you might normally experience after taking a full breath. You will need to exhale completely, hold your nose tightly closed, and then take a full and complete inhalation from the self-administration mask. Please hold this breath for four seconds after you finish the inhalation. I will count to four for you. Let’s do a practice trial to make sure you understood the procedure. After you hold the breath for the four seconds and then exhale, I will hand you a brief form to complete immediately after you have exhaled the gas. Do you have any questions?”

Whereas, participants assigned to the Expected Relaxation condition received the following instructions:

- “this study investigates the effects of carbon dioxide inhalation on mood. You will be taking a double vital capacity breath containing either 35% carbon dioxide and 65% oxygen or normal room air. Breathing the carbon dioxide mixture may result in various physical feelings of relaxation, such as lightheadedness, a slight tingling in the extremities, or a sense of floating or being detached from your body. Breathing in the room air will not result in any different physical feelings besides those you might normally experience after taking a full breath. You will need to exhale completely, hold your nose tightly closed, and then take a full and complete inhalation from the self-administration mask. Please hold this breath for four seconds after you finish the inhalation. I will count to four for you. Let’s do a practice trial to make sure you understand the procedure. After you hold the breath for

the four seconds and then exhale, I will hand you a form to fill out. Do you have any questions?”

To verify if the participant had understood the instruction, immediately after reading the instruction, the researcher asked: "The instructions that I have just read, say that the inhalation of CO_2 can produce various physical sensations of arousal or relaxation?" (when the assigned instruction was the Expected Arousal), or "The instructions that I have just read, say that the inhalation of CO_2 can produce various physical sensations of relaxation or arousal? "(when the assigned instruction was the Expected Relaxation). The subjects chose between two answers: “relaxation” or “arousal”.

5. Statistical analysis

First, an analysis of descriptive variables was run. The frequencies of dichotomous, nominal, and ordinal variables (i.e., gender, marital status, type of employment, and educational level) were calculated as well as mean and standard deviation of continuous variables (i.e., age, amount of inhaled CO_2 and room air, VAAS, VAS-F, VAS-D, PSL, ASI-3, SSAS, IAS, BAI, BDI, STAY). The sample was stratified according to the level of anxiety sensitivity using as a cut-off the mean (SD) of the ASI-3 observed in the Italian general population (Petrocchi et al., 2015). Thus, subjects with a ASI-3 total score $\leq$ 11.21 (8.68) for males and $\leq$ 12.93 (9.55) for females were assigned to the low AS group (LAS) while subjects with ASI-3 total score $\geq$ 11.21 (8.68) for males and $\geq$ 12.93 (9.55) for females were assigned to the high AS group (HSA).

The baseline scores among the four groups (i.e., HAS-EA, HAS-ER, LAS-EA, LAS-ER) were compared using the Kruskal-Wallis test and Mann-Whitney test for continuous data; the Chi-square test was used for categorical variables.

The response to the challenge (i.e., 35% CO_2 *versus* room air inhalation) was evaluated calculating delta scores (post-test *minus* pre-test score) of each rating scale (i.e., VAAS, VAS-F, VAS-D, PSL) and psychophysiological measurements (i.e., blood pressure, heart rate). Delta scores comparison were run via the Wilcoxon test for dependent sample.

The Chi-square test was used to compare the frequency of panic attacks occurred as a response to the challenge (panic attack occurred when an increased from pre-test to post-test of 25 units for VAAS and an increased of at least 4 vegetative symptoms in PSL were observed) in the four groups.

The effects of the double inhalation (CO_2 *versus* room air), of the assigned instruction (Expected Arousal *versus* Expected Relaxation), or of AS (high AS *versus* low AS) on participants' emotional response to the challenge were analyzed by means of the Wilcoxon test for dependent samples. The Mann-Whitney test for independent samples was used to evaluate the presence of statistically

significant differences between the two sets of instructions and between HAS and LAS on the psychological (i.e., VAAS, VAS-F, VAS-D, PSL) and psychophysiological measures.

Hierarchical multiple regression analysis was used to determine the independent and combined effects of AS (high AS *versus* low AS), instructional set (Expected Arousal *versus* Expected Relaxation), and gas mixture inhaled (CO_2 *versus* room air) on the anxiety response to the challenge. Post-test scores of VAAS, VAS-F, VAS-D, and PSL were separately used as dependent variable. At Step 1, the pre-test score of each dependent variable was used. At Step 2, in order to adjust for affectivity and hypochondriacal belief, baseline score of IAS, BAI, BDI, and STAI-1 were entered. The level of anxiety sensitivity was entered at Step 3. The randomized instructions were entered at Step 4. The sequence of gas mixture administration was entered at Step 5 and the gas mixture was entered at Step 6.

Statistically significance was set at $p \leq 0.05$. The statistical analyses were run via the Statistical Package for Social Sciences 20 (SPSS).

Chapter 3. Results

1. Descriptive analysis

1.1. Sample characteristics

The sample was composed by 68 subjects, 40 females (58.8%) and 28 males (41.2%); thus, we obtained 34 couples of subjects, matched for age, sex, and baseline level of AS. Mean age for the total sample was 25.46 ± 6.77 years (mean age for females was 26.58 ± 8.27 and for males was 23.86 ± 3.25 years). Sixty-five subjects were single (95.6%) and 3 had a partner (4.4%). Concerning the educational level, 10 subjects (14.7%) had the Master degree, 27 (39.7%) had the Bachelor degree, 29 (42.6%) had the high-school diploma, and 2 (2.9%) completed the secondary school. Fifty-two subjects (76.5%) were students, 8 (11.8%) were blue-collar workers, 5 (7.4%) were white-collar, 2 (2.9%) were housewife, and 1 (1.5%) was retired. Concerning the smoking status, 39 subjects (57.4%) were no-smokers, 20 (29.4%) were smokers, and 9 (13.2%) were former smokers. Among smokers, the average number of cigarettes smoked per day was 8.3 ± 5.75.

The sample was stratified for the level of AS, using as cut-off points the mean of ASI-3 total score of the Italian general population (Petrocchi et al., 2015). Thirty-four subjects (50%) had a high level of AS (HAS), among them 20 were females while 34 (50%) had a low level of AS (LAS) (females n= 20). Comparing subjects with HAS and LAS no statistically significant differences were found for social status and working activity (Table 1). Table 2 reports the mean score and standard deviation (SD) of the ASI-3 (total score, subscale scores).

Table 1. Comparison between HAS and LAS for social status and working activity. Chi-square test for independent samples

	HAS (n = 34)	**LAS (n = 34)**	χ^2	*p*
Social Status				
Single	33	32	1.333	0.513
Married	1	2		
Total	34	34		
Working activity				
Students	27	25	5.910	0.433
Blue-collar	3	5		
White-collar	2	3		
Housewife	2	0		
Ritired	0	1		
Total	34	34		

Note. HAS = high anxiety sensitivity; LAS= low anxiety sensitivity.

Table 2. ASI-3 total score and subscale scores. Comparison between HAS and LAS groups. Mann-Whitney test for independent samples

Baseline assessment	**HAS (n = 34)**	**LAS (n = 34)**	
	M ± SD	**M ± SD**	*p*
ASI-3 total	18.29 ± 4.945	5.29 ± 3.186	**0.000**
ASI-3 Physical concern	5.79 ± 2.847	1.62 ± 1.538	**0.000**
ASI-3 Cognitive concern	3.91 ± 2.832	0.50 ± 0.961	**0.000**
ASI-3 Social concern	8.59 ± 3.710	3.18 ± 2.393	**0.000**

Note. ASI-3= Anxiety Sensitivity Index-3; HAS= high anxiety sensitivity ; LAS= low anxiety sensitivity.

Therefore, 34 subjects (50%) were randomized to Expected Arousal instructions (EA) and 34 (50%) were randomized to Expected Relaxation instructions (ER). Comparing the 4 experimental groups (HAS-EA, HAS-ER, LAS-EA, LAS-ER), no statistically significant differences were found concerning social status, working activity, vital capacity, and volume inhaled at the first and second inhalation (Table 3.1 and Table 3.2).

Table 3.1. Comparison among HAS-EA, HAS-ER, LAS-EA, and LAS-ER for social status and working activity. Chi-square test

	HAS-EA (n= 17)	HAS-ER (n= 17)	LAS-EA (n= 17)	LAS-ER (n= 17)	χ^2	*p*
Social Status						
Single	17	15	17	15	6.917	0.329
Married	0	2	0	2		
Total	17	17	17	17		
Working activity						
Students	15	10	14	13	20.744	0.293
Blue-collar	2	3	2	1		
White-collar	0	3	1	1		
Housewife	0	0	0	2		
Ritired	0	1	0	0		
Total	17	17	17	17		

Note. HAS-EA= high anxiety sensitivity - expected arousal; HAS-ER= high anxiety sensitivity - expected relaxation; LAS-EA= low anxiety sensitivity - expected arousal; LAS-ER= low anxiety sensitivity - expected relaxation.

Table 3.2. Comparison among HAS-EA, HAS-ER, LAS-EA, and LAS-ER for vital capacity and volume inhaled at the first and second inhalation. Kruskal-Wallis for independent samples

	HAS-EA (n= 17)	HAS-ER (n= 17)	LAS-EA (n= 17)	LAS-ER (n= 17)	*p*
Vital capacity	2.82 ± 1.286	3.47 ± 0.717	3.18 ± 1.468	3.35 ± 1.115	0.421
Volume inhaled - 1° inhalation	4.11 ± 1.755	4.12 ± 1.352	4.72 ± 2.127	4.49 ± 1.697	0.769
Volume inhaled - 2° inhalation	3.94 ± 1.769	4.24 ± 1.428	4.59 ± 2.038	4.84 ± 1.852	0.556

Note. HAS-EA= high anxiety sensitivity - expected arousal; HAS-ER= high anxiety sensitivity - expected relaxation; LAS-EA= low anxiety sensitivity - expected arousal; LAS-ER= low anxiety sensitivity - expected relaxation.

Table 4 reports mean and SD of ASI-3 total and subscale scores for the four experimental groups (HAS-EA, HAS-ER, LAS-EA, LAS-ER). As expected, the HAS-EA group and the HAS-ER group had statistically significant higher scores compared to the LAS-EA group and to the LAS-ER group. Comparing each pair of subgroups via the Mann-Whitney test for independent sample, we found no statistically significant differences between HAS-EA and HAS-ER groups; a statistically

significant higher score for ASI-3 Cognitive Concern in LAS-EA compared to LAS-ER (*U*=74.500; *p*=0.003); HAS-EA had statistically significant higher scores for ASI-3 total (*U*=0.000; *p*=0.000), Physical concern (*U*=44.000; *p*=0.000), Cognitive concern (*U*=60.500; *p*=0.003), and Social concern (*U*=21.500; *p*=0.000) subscale scores if compared to LAS-EA; HAS-ER had statistically significant higher scores for ASI-3 total (*U*=0.000; *p*=0.000), Physical concern (*U*=30.000; *p*=0.000), Cognitive concern (*U*=25.000; *p*=0.000), and Social concern (*U*=16.500; *p*=0.000) subscale scores if compared to LAS-EA. HAS-EA had statistically significant higher scores for ASI-3 total (*U*=0.500; *p*=0.000), Physical concern (*U*=41.000; *p*=0.000), Cognitive concern (*U*=20.000; *p*=0.000), and Social concern (*U*=47.000; *p*=0.001) subscale scores if compared to LAS-ER; HAS-ER had all statistically significant higher scores for ASI-3 total (*U*=0.500; *p*=0.000), Physical concern (*U*=24.000; *p*=0.000), Cognitive concern (*U*=9.000; *p*=0.000), and Social concern (*U*=34.500; *p*=0.000) subscale scores if compared to LAS-ER.

Table 4. ASI-3 total score and subscale scores. Comparison among HAS-EA, HAS-ER, LAS-EA, and LAS-ER groups. Kruskal-Wallis test for independent sample

Baseline assessment	**HAS-EA (n= 17)**	**HAS-ER (n= 17)**	**LAS-EA (n= 17)**	**LAS-ER (n= 17)**	
	M ± SD	**M ± SD**	**M ± SD**	**M ± SD**	***p***
ASI-3 total	16.76 ± 2.990	19.82 ± 6.044	5.53 ± 2.741	5.06 ± 3.648	**0.000**
ASI-3 Physical concern	5.59 ± 2.980	6.00 ± 2.784	1.71 ± 1.532	1.53 ± 1.586	**0.000**
ASI-3 Cognitive concern	3.18 ± 2.481	4.65 ± 3.040	0.94 ± 1.197	0.06 ± 0.243	**0.000**
ASI-3 Social concern	8.00 ± 3.708	9.18 ± 3.729	2.88 ± 1.799	3.47 ± 2.896	**0.000**

Note. HAS-EA= high anxiety sensitivity - expected arousal; HAS-ER= high anxiety sensitivity - expected relaxation; LAS-EA= low anxiety sensitivity - expected arousal; LAS-ER= low anxiety sensitivity - expected relaxation; ASI-3 = Anxiety Sensitivity Index -3.

Table 5 shows the comparison among the four groups concerning clinical variables measured at baseline. No statistically significant differences were observed for physiological measures (i.e., blood pressure and heart rate).

Comparing each pair of subgroups via the Mann-Whitney test for independent sample, HAS-ER showed a statistically significant higher score for IAS-Tanatophobia (U=86.500; p=0.045) compared to HAS-EA. HAS-EA group showed statistically significant higher scores for IAS total (U=48.000; p=0.001), IAS-Worry about Illness (U=69.500; p=0.009), IAS-Concern about Pain (U=86.000; p=0.045), IAS-Tanatophobia (U=81.500; p=0.029), IAS-Bodily Preoccupations (U=77.000; p=0.020), BAI (U=53.500; p=0.001), BDI (U=65.000; p=0.005), STAI-1 (U=69.500; p=0.009), and STAI-2 (U=38.500; p=0.000) if compared to LAS-EA. HAS-ER group showed statistically significant higher scores for IAS total (U=45.000; p=0.000), IAS - Worry about Illness (U=83.500; p=0.032), IAS-Concern about Pain (U=81.500; p=0.029), IAS-Tanatophobia (U=41.500; p=0.000), IAS-Disease Phobia (U=64.000; p=0.005), IAS-Bodily Preoccupations (U=63.500; p=0.004), IAS-Effects of Symptoms (U=83.000; p=0.034), BDI (U=61.000; p=0.003), and STAI-2 (U=40.500; p=0.000) if compared to LAS-EA. HAS-EA group showed statistically significant higher scores for SSAS (U=83.000; p=0.034), IAS total (U=52.000; p=0.001), IAS - Worry about Illness (U=68.000; p=0.008), IAS-Concern about Pain (U=87.500; p=0.049), IAS-Tanatophobia (U=80.000; p=0.026), IAS-Bodily Preoccupations (U=75.000; p=0.016), BAI (U=45.000; p=0.001), BDI (U=78.000; p=0.022), STAI-1 (U=85.000; p=0.040), and STAI-2 (U=49.500; p=0.001) if compared to LAS-ER. HAS-ER group showed statistically significant higher scores for SSAS (U=84.000; p=0.035), IAS total (U=48.000; p=0.001), IAS - Worry about Illness (U=83.500; p=0.033), IAS-Tanatophobia (U=38.500; p=0.000), IAS-Disease Phobia (U=63.000; p=0.004), IAS-Bodily Preoccupations (U=59.500; p=0.003), BAI (U=86.500; p=0.045), BDI (U=79.000; p=0.022), and STAI-2 (U=49.500; p=0.001) if compared to LAS-ER. Comparing LAS-EA and LAS-ER groups no statistically significant differences were found.

Table 5. Mean and SD for baseline measures. Comparison among HAS-EA, HAS-ER, LAS-EA, and LAS-ER groups. Kruskal-Wallis test for independent samples

Baseline assessment	**HAS-EA (n= 17)**	**HAS-ER (n= 17)**	**LAS-EA (n= 17)**	**LAS-ER (n= 17)**	
	M ± SD	**M ± SD**	**M ± SD**	**M ± SD**	***p***
SSAS	23.94 ± 4.479	23.53 ± 3.204	21.12 ± 5.847	20.59 ± 4.611	0.056
IAS	29.71 ± 9.923	32.29 ± 9.713	19.76 ± 4.906	19.88 ± 6.936	**0.000**
IAS-Worry about Illness	6.24 ± 2.306	5.76 ± 1.821	4.41 ± 1.326	4.18 ± 1.845	**0.007**
IAS-Concern about Pain	4.88 ± 2.690	4.71 ± 2.285	3.29 ± 1.047	3.06 ± 2.487	**0.036**
IAS-Health Habits	5.65 ± 2.548	6.29 ± 2.733	4.94 ± 2.585	5.71 ± 2.392	0.470
IAS-Hypochondriacal Beliefs	0.65 ± 1.272	0.35 ± 0.493	0.18 ± 0.728	0.12 ± 0.485	**0.049**
IAS-Thanatophobia	3.00 ± 2.151	4.76 ± 2.682	1.41 ± 1.278	1.29 ± 1.572	**0.000**
IAS-Disease Phobia	1.18 ± 1.334	2.29 ± 2.144	0.53 ± 1.068	0.47 ± 0.874	**0.003**
IAS-Bodily Preoccupations	3.24 ± 1.522	3.76 ± 1.786	2.00 ± 1.323	2.00 ± 1.225	**0.002**
IAS-Treatment Experiences	3.65 ± 1.766	2.88 ± 2.027	2.59 ± 1.460	2.76 ± 1.393	0.310
IAS-Effects of Symptoms	1.24 ± 1.480	3.47 ± 8.790	0.41 ± 1.064	2.82 ± 7.443	**0.043**
BAI	10.29 ± 5.531	7.29 ± 3.077	5.00 ± 3.708	4.88 ± 2.934	**0.001**
BDI	4.00 ± 3.162	4.65 ± 3.952	1.47 ± 2.503	2.18 ± 3.432	**0.003**
STAI-1	38.00 ± 8.404	37.71 ± 9.479	30.59 ± 6.681	33.29 ± 5.665	**0.030**
STAI-2	39.94 ± 5.166	40.88 ± 7.227	32.35 ± 4.873	33.29 ± 5.253	**0.000**
Systolic blood pressure	122.35 ± 17.157	126.18 ± 14.192	119.35 ± 11.784	128.65 ± 16.515	0.416
Diastolic blood pressure	72.59 ± 7.177	71.59 ± 9.586	68.94 ± 7.172	73.53 ± 12.880	0.658
Heart rate	75.35 ± 14.309	71.35 ± 9.886	74.53 ± 18.180	72.53 ± 13.314	0.812

Note. SSAS= Somatosensory Amplification Scale; IAS= Illness Attitude Scales; BAI= Beck Anxiety Inventory; BDI= Beck Depression Inventory; STAI-1= State Trait Anxiety Inventory - State; STAI-2= State Trait Anxiety Inventory - Trait; HAS-EA= high anxiety sensitivity - expected arousal; HAS-ER= high anxiety sensitivity - expected relaxation; LAS-EA= low anxiety sensitivity - expected arousal; LAS-ER= low anxiety sensitivity - expected relaxation.

2. Pre-test comparison

Table 6 shows the comparison between HAS and LAS concerning psychological (i.e., VAAS, VAS-F, VAS-D, PSL) and physiological variables (i.e., blood pressure and heart rate) as measured at pre-test. A statistically significant difference was found for PSL (U = 1539.000; p = 0.000) while no statistically significant differences were observed for VAAS, VAS-F, and VAS-D, as well as for physiological variables (i.e., blood pressure and heart rate).

Table 6. Mean and SD for pre-test measures. Comparison between HAS and LAS. Mann-Whitney test for independent samples

Pre-test	**HAS (n=34)**	**LAS (n= 34)**	
	M ± SD	**M ± SD**	***p***
VAAS	10.87 ± 14.559	12.71 ± 15.481	0.598
VAS-F	5.78 ± 13.115	4.40 ± 8.199	0.766
VAS-D	7.57 ± 11.377	8.72 ± 13.747	0.538
PSL	1.76 ± 2.103	0.66 ± 0.924	**0.000**
Systolic blood pressure	126.51 ± 14.846	123.75 ± 20.853	0.659
Diastolic blood pressure	74.51 ± 6.748	72.63 ± 9.452	0.073
Heart Rate	75.04 ± 11.125	72.66 ± 13.021	0.362

Note. VAAS= Visual Analogue Scale of Anxiety; VAS-F= Visual Analogue Scale of Fear; VAS-D= Visual Analogue Scale of Discomfort; PSL= Panic Symptom List; HAS= high anxiety sensitivity group; LAS= low anxiety sensitivity group.

Table 7 shows the comparison among the four groups. A statistically significant difference was observed for PSL (H(3) = 14.921; p = 0.002); no statistically significant differences were observed for VAAS, VAS-F, and VAS-D, and for physiological variables (i.e., blood pressure and heart rate). Comparing each pair of subgroups via the Mann-Whitney test for independent samples, HAS-EA showed statistically significant higher score for PSL (U = 388.000; p = 0.009) compared to the LAS-EA and LAS-ER (U = 295.000; p = 0.000).

Table 7. Mean and SD for pre-test measures. Comparison between HAS-EA, HAS-ER, LAS-EA, and LAS-ER groups. Kruskal-Wallis test for independent samples

Pre-test	**HAS-EA (n= 17)**	**HAS-ER (n= 17)**	**LAS-EA (n= 17)**	**LAS-ER (n= 17)**	
	M ± SD	**M ± SD**	**M ± SD**	**M ± SD**	***p***
VAAS	11.26 ± 12.870	10.47 ± 16.260	14.37 ± 17.424	10.94 ± 13.153	0.422
VAS-F	5.76 ± 13.574	5.79 ± 12.844	5.63 ± 9.490	3.09 ± 6.454	0.349
VAS-D	8.35 ± 12.269	6.79 ± 10.536	8.89 ± 13.488	8.55 ± 14.224	0.637
PSL	1.82 ± 1.898	1.71 ± 2.316	0.80 ± 1.023	0.52 ± 0.795	**0.002**
Systolic blood pressure	128.15 ± 17.06	124.88 ± 12.274	120.83 ± 13.546	126.85 ± 26.387	0.132
Diastolic blood pressure	73.85 ± 8.367	75.18 ± 4.642	70.54 ± 6.866	74.85 ± 11.275	0.056
Heart rate	74.21 ± 12.489	75.88 ± 9.688	73.29 ± 13.883	72.00 ± 12.219	0.657

Note. VAAS= Visual Analogue Scale of Anxiety; VAS-F= Visual Analogue Scale of Fear; VAS-D= Visual Analogue Scale of Discomfort; PSL= Panic Symptom List; HAS-EA= high anxiety sensitivity - expected arousal; HAS-ER= high anxiety sensitivity - expected relaxation; LAS-EA= low anxiety sensitivity - expected arousal; LAS-ER= low anxiety sensitivity - expected relaxation.

3. Post-test comparison

Table 8 shows the comparison between HAS and LAS concerning psychological (i.e., VAAS, VAS-F, VAS-D, PSL) and physiological variables (i.e., blood pressure and heart rate) as measured at post-test. No statistically significant differences were found.

Table 8. Mean and SD for post-test measures. Comparison between HAS and LAS. Mann-Whitney test for independent samples

Post-test	**HAS (n=34)**	**LAS (n= 34)**	
	M ± SD	**M ± SD**	***p***
VAAS	18.59 ± 20.595	21.78 ± 22.511	0.434
VAS-F	14.81 ± 19.944	15.31 ± 20.116	0.842
VAS-D	18.24 ± 22.781	20.43 ± 25.109	0.737
PSL	5.15 ± 5.334	4.15 ± 4.453	0.355
Systolic blood pressure	129.85 ± 16.006	128.25 ± 15.204	0.629
Diastolic blood pressure	74.32 ± 9.101	73.43 ± 10.881	0.290
Heart Rate	76.25 ± 11.593	72.91 ± 12.876	0.219

Note. VAAS= Visual Analogue Scale of Anxiety; VAS-F= Visual Analogue Scale of Fear; VAS-D= Visual Analogue Scale of Discomfort; PSL= Panic Symptom List; HAS= high anxiety sensitivity; LAS= low anxiety sensitivity.

Table 9 shows the comparison among the four groups concerning psychological (i.e., VAAS, VAS-F, VAS-D, PSL) and physiological variables (i.e., blood pressure and heart rate) as measured at post-test. No statistically significant differences were found.

Table 9. Mean and SD for post-test measures. Comparison among HAS-EA, HAS-ER, LAS-EA, and LAS-ER groups. Kruskal-Wallis test for independent samples

Post-test	HAS-EA (n= 17)	HAS-ER (n= 17)	LAS-EA (n= 17)	LAS-ER (n= 17)	
	M ± SD	**M ± SD**	**M ± SD**	**M ± SD**	***p***
VAAS	18.68 ± 22.679	18.50 ± 18.632	23.49 ± 25.475	19.97 ± 19.102	0.833
VAS-F	15.79 ± 22.324	13.82 ± 17.528	19.20 ± 23.067	11.18 ± 15.739	0.733
VAS-D	17.68 ± 23.333	18.79 ± 22.552	22.40 ± 28.514	18.33 ± 21.151	0.908
PSL	5.53 ± 5.647	4.76 ± 5.058	4.43 ± 5.095	3.85 ± 3.709	0.816
Systolic blood pressure	131.74 ± 19.698	127.97 ± 11.172	123.91 ± 12.434	132.85 ± 16.655	0.056
Diastolic blood pressure	73.15 ± 11.521	75.50 ± 5.706	70.86 ± 6.766	76.15 ± 13.579	0.069
Heart rate	74.88 ± 13.352	77.62 ± 9.525	71.57 ± 12.453	74.33 ± 13.353	0.272

Note. VAAS= Visual Analogue Scale of Anxiety; VAS-F= Visual Analogue Scale of Fear; VAS-D= Visual Analogue Scale of Discomfort; PSL= Panic Symptom List; HAS-EA= high anxiety sensitivity - expected arousal; HAS-ER= high anxiety sensitivity - expected relaxation; LAS-EA= low anxiety sensitivity - expected arousal; LAS-ER= low anxiety sensitivity - expected relaxation.

Comparing the four experimental groups (HAS-EA, HAS-ER, LAS-EA, LAS-ER) on the number of panic attack occurred as a response to the challenge, no statistically differences were found (Table 10).

Table 10. Panic attack indices in response to CO_2 and room air inhalation. Comparison among HAS-EA, HAS-ER, LAS-EA, and LAS-ER groups. Chi-square test

Panic	**HAS-EA (n= 17)**	**HAS-ER (n= 17)**	**LAS-EA (n= 17)**	**LAS-ER (n= 17)**	χ^2	***p***
CO_2						
Yes	5	5	4	3	14.345	0.834
No	12	12	13	14		
Total	17	17	17	17		
Room air						
Yes	0	0	1	0	18.678	0.892
No	17	17	16	17		
Total	17	17	17	17		

Note. CO_2 = carbon dioxide; HAS-EA= high anxiety sensitivity - expected arousal; HAS-ER= high anxiety sensitivity - expected relaxation; LAS-EA= low anxiety sensitivity - expected arousal; LAS-ER= low anxiety sensitivity - expected relaxation.

4. Effects of the challenge, anxiety sensitivity and instructions

Delta scores (post-test *minus* pre-test score) of psychological (i.e., VAAS, VAS-F, VAS-D, PSL) and physiological measures (i.e., blood pressure, heart rate) were calculated. Comparing delta scores under CO_2 and under room air, a statistically significant higher response on the VAAS, VAS-F, VAS-D, and PSL were found under CO_2 inhalation while no statistically significant results were found for blood pressure and heart rate (Table 11).

Table 11. Delta (post- *minus* pre-test) scores of psychological and physiological variables. CO_2 inhalation *versus* room air. Wilcoxon test for dependent sample

	CO_2	**Room air**	
Post-test *minus* Pre-test	**M ± SD**	**M ± SD**	***p***
delta VAAS	16.62 ± 24.125	0.18 ± 11.279	**0.000**
delta VAS-F	17.22 ± 22.074	2.72 ± 13.554	**0.000**
delta VAS-D	22.01 ± 23.848	0.35 ± 9.941	**0.000**
delta PSL	6.68 ± 4.780	0.25 ± 1.687	**0.000**
delta Systolic blood pressure	6.06 ± 15.584	1.78 ± 7.560	0.101
delta Diastolic blood pressure	0.84 ± 7.759	- 0.24 ± 5.289	0.282
delta Heart Rate	0.71 ± 8.677	0.75 ± 6.247	0.881

Note. Delta VAAS= delta Visual Analogue Scale of Anxiety; delta VAS-F= delta Visual Analogue Scale of Fear; delta VAS-D= delta Visual Analogue Scale of Discomfort; delta PSL= delta Panic Symptom List; CO_2 = carbon dioxide.

Table 12 shows delta scores comparison between HAS and LAS groups. Considering the psychological variables, a statistically significant difference was found for VAS-F delta score: LAS group reported higher fear response after room air inhalation, compared to HAS group. No statistically significant differences were observed for VAAS, VAS-D, and PSL and physiological measures (i.e., blood pressure and heart rate).

Table 12. Delta (post- *minus* pre-test) scores comparison between HAS group and LAS group, according to the gas inhalation mixture (CO_2 *versus* room air). Mann-Whitney test for independent samples

		HAS group	LAS group	
Post-test *minus* Pre-test		**M ± SD**	**M ± SD**	***p***
delta VAAS	CO_2	15.68 ± 26.545	17.56 ± 21.799	0.469
	Room air	-0.23 ± 10.392	0.59 ± 12.245	0.843
delta VAS-F	CO_2	18.29 ± 23.726	16.15 ± 20.591	0.951
	Room air	-0.23 ± 14.121	5.68 ± 12.475	**0.032**
delta VAS-D	CO_2	22.73 ± 24.045	21.29 ± 23.989	0.764
	Room air	-1.41 ± 8.24	2.12 ± 11.243	0.166
delta PSL	CO_2	6.94 ± 5.382	6.41 ± 4.157	0.721
	Room air	-0.18 ± 1.623	0.68 ± 1.664	0.057
delta Systolic blood pressure	CO_2	5.97 ± 8.558	6.15 ± 20.489	0.326
	Room air	0.71 ± 7.748	2.85 ± 7.324	0.344
delta Diastolic blood pressure	CO_2	1.18 ± 8.799	0.50 ± 6.675	0.597
	Room air	-1.559 ± 5.206	1.09 ± 5.107	0.069
delta Heart Rate	CO_2	1.76 ± 8.791	-0.35 ± 8.559	0.454
	Room air	0.65 ± 7.027	0.85 ± 5.461	0.511

Note. Delta VAAS= delta Visual Analogue Scale of Anxiety; delta VAS-F= delta Visual Analogue Scale of Fear; delta VAS-D= delta Visual Analogue Scale of Discomfort; delta PSL= delta Panic Symptom List; CO_2 = carbon dioxide.CO_2 = carbon dioxide; HAS= high anxiety sensitivity group; LAS= low anxiety sensitivity group.

Stratifying for anxiety sensitivity, HAS group showed a statistically significant result for delta VAAS, VAS-F, VAS-D, PSL, and systolic blood pressure under CO_2 inhalation compared to room air. No statistically significant differences were found for diastolic blood pressure and heart rate (Table 13).

Table 13. HAS group delta (post- *minus* pre-test) scores of psychological and physiological variables. CO_2 condition *versus* room air. Wilcoxon test for dependent samples

	HAS Group		
	CO_2	**Room air**	
Post-test *minus* Pre-test	**M ± SD**	**M ± SD**	***p***
delta VAAS	15.68 ± 26.545	-0.23 ± 10.392	**0.002**
delta VAS-F	18.29 ± 23.726	-0.23 ± 14.121	**0.001**
delta VAS-D	22.73 ± 24.045	-1.41 ± 8.24	**0.000**
delta PSL	6.94 ± 5.382	-0.18 ± 1.623	**0.000**
delta Systolic blood pressure	5.97 ± 8.558	0.71 ± 7.748	**0.012**
delta Diastolic blood pressure	1.18 ± 8.799	-1.559 ± 5.206	0.058
delta Heart Rate	1.76 ± 8.791	0.65 ± 7.027	0.601

Note. Delta VAAS= delta Visual Analogue Scale of Anxiety; delta VAS-F= delta Visual Analogue Scale of Fear; delta VAS-D= delta Visual Analogue Scale of Discomfort; delta PSL= delta Panic Symptom List; CO_2 = carbon dioxide; HAS= high anxiety sensitivity group.

LAS group showed a statistically significant result for delta VAAS, VAS-F, VAS-D, and PSL under CO_2 inhalation compared to room air. No statistically significant differences were found for blood pressure and heart rate (Table 14).

Table 14. LAS group delta (post- *minus* pre-test) scores of psychological and physiological variables. CO_2 condition *versus* room air. Wilcoxon test for dependent samples

	LAS Group		
	CO_2	**Room air**	
Post-test *minus* Pre-test	**M ± SD**	**M ± SD**	***p***
delta VAAS	17.56 ± 21.799	0.59 ± 12.245	**0.000**
delta VAS-F	16.15 ± 20.591	5.68 ± 12.475	**0.005**
delta VAS-D	21.29 ± 23.989	2.12 ± 11.243	**0.000**
delta PSL	6.41 ± 4.157	0.68 ± 1.664	**0.000**
delta Systolic blood pressure	6.15 ± 20.489	2.85 ± 7.324	0.858
delta Diastolic blood pressure	0.50 ± 6.675	1.09 ± 5.107	0.620
delta Heart Rate	-0.35 ± 8.559	0.85 ± 5.461	0.452

Note. Delta VAAS= delta Visual Analogue Scale of Anxiety; delta VAS-F= delta Visual Analogue Scale of Fear; delta VAS-D= delta Visual Analogue Scale of Discomfort; delta PSL= delta Panic Symptom List; CO_2 = carbon dioxide; LAS= low anxiety sensitivity group.

Delta scores comparison between Expected Arousal group and Expected Relaxation group was run. No statistically significant differences were observed for psychological (i.e., VAAS, VAS-F, VAS-D, PSL) and physiological measures (i.e., blood pressure and heart rate) (Table 15).

Table 15. Delta (post- *minus* pre-test) scores comparison between Expected Arousal group and Expected Relaxation group, per gas inhalation mixture (CO_2 *versus* room air). Mann-Whitney test for independent samples

		EA group	ER group	
Post-test *minus* Pre-test		**M ± SD**	**M ± SD**	***p***
delta VAAS	CO_2	16.76 ± 24.832	16.47 ± 23.769	0.704
	Room air	0.03 ± 10.503	0.32 ± 12.162	0.600
delta VAS-F	CO_2	18.85 ± 24.236	15.59 ± 19.910	0.995
	Room air	5.15 ± 15.815	0.29 ± 10.524	0.426
delta VAS-D	CO_2	21.94 ± 25.147	22.09 ± 22.855	0.941
	Room air	1.29 ± 9.793	-0.59 ±10.145	0.632
delta PSL	CO_2	7.21 ± 4.798	6.15 ± 4.775	0.393
	Room air	0.35 ± 1.998	0.15 ± 1.329	0.950
delta Systolic blood pressure	CO_2	4.26 ± 10.097	7.85 ± 19.608	0.576
	Room air	1.94 ± 7.438	1.62 ± 7.789	0.902
delta Diastolic blood pressure	CO_2	0.64 ± 8.745	1.03 ± 6.758	0.495
	Room air	-1.26 ± 5.299	0.79 ± 5.151	0.168
delta Heart Rate		-0.73 ± 10.561	2.15 ±6.086	0.080
	Room air	-0.56 ± 5.321	2.06 ± 6.884	0.063

Note. Delta VAAS= delta Visual Analogue Scale of Anxiety; delta VAS-F= delta Visual Analogue Scale of Fear; delta VAS-D= delta Visual Analogue Scale of Discomfort; delta PSL= delta Panic Symptom List; CO_2 = carbon dioxide.CO_2 = carbon dioxide; EA= Expected Arousal group; ER= Expected Relaxation group.

Stratifying for the two sets of instructions, EA and ER groups showed a statistically significant result for delta VAAS, VAS-F, VAS-D, and PSL under CO_2 inhalation compared to room air. No

statistically significant differences were found for physiological measures (i.e., blood pressure and heart rate) (Table 16 and 17).

Table 16. EA group delta (post- *minus* pre-test) scores of psychological and physiological variables. CO_2 condition *versus* room air. Wilcoxon test for dependent samples

	EA Group		
	CO_2	**Room air**	
Post-test *minus* Pre-test	**M ± SD**	**M ± SD**	***p***
delta VAAS	16.76 ± 24.832	0.03 ± 10.503	**0.001**
delta VAS-F	18.85 ± 24.236	5.15 ± 15.815	**0.011**
delta VAS-D	21.94 ± 25.147	1.29 ± 9.793	**0.000**
delta PSL	7.21 ± 4.798	0.35 ± 1.998	**0.000**
delta Systolic blood pressure	4.26 ± 10.097	1.94 ± 7.438	0.391
delta Diastolic blood pressure	0.64 ± 8.745	-1.26 ± 5.399	0.175
delta Heart Rate	-0.73 ± 10.561	-0.56 ± 5.321	0.886

Note. Delta VAAS= delta Visual Analogue Scale of Anxiety; delta VAS-F= delta Visual Analogue Scale of Fear; delta VAS-D= delta Visual Analogue Scale of Discomfort; delta PSL= delta Panic Symptom List; CO_2 = carbon dioxide; EA= expected arousal group.

Table 17. ER group delta (post- *minus* pre-test) scores of psychological and physiological variables. CO_2 condition *versus* room air. Wilcoxon test for dependent samples

	ER Group		
	CO_2	**Room air**	
Post-test *minus* Pre-test	**M ± SD**	**M ± SD**	***p***
delta VAAS	16.47 ± 23.769	0.32 ± 12.162	**0.001**
delta VAS-F	15.59 ± 19.910	0.29 ± 10.524	**0.000**
delta VAS-D	22.09 ± 22.855	-0.59 ± 10.145	**0.000**
delta PSL	6.15 ± 4.775	0.15 ± 1.329	**0.001**
delta Systolic blood pressure	7.85 ± 19.608	1.62 ± 7.789	0.132
delta Diastolic blood pressure	1.03 ± 6.758	0.79 ± 5.151	0.907
delta Heart Rate	2.15 ± 6.086	2.06 ± 6.884	0.644

Note. Delta VAAS= delta Visual Analogue Scale of Anxiety; delta VAS-F= delta Visual Analogue Scale of Fear; delta VAS-D= delta Visual Analogue Scale of Discomfort; delta PSL= delta Panic Symptom List; CO_2 = carbon dioxide; ER= expected relaxation group.

5. Combined effects of anxiety sensitivity, expectancy manipulation, and gas mixture on panic-like response

A six stage hierarchical multiple regression was conducted with each post-test score separately (i.e., VAAS, VAS-F, VAS-D, PSL, systolic blood pressure, diastolic blood pressure, heart rate) as dependent variable. The corresponding each pre-test score was entered at step 1 of the regression model. The baseline score for IAS, BAI, BDI, and STAI-1 were entered at step 2. The level of anxiety sensitivity was entered at step 3. The randomized instructions were entered at step 4. The sequence of gas mixture administration was entered at step 5, and gas mixture was entered at step 6.

In table 18 the results of hierarchical multiple regression for psychological variables are presented.

- VAAS: the predictor variables collectively explained 36.5% of the overall variance ($F(9, 58) = 8.05$, $p = .000$). Step 1 variable accounted for 17.4% (adjusted $R_2 = 0.168$) of the variance ($F(1, 66) = 28.17$, $p = .000$). Step 2 variable (baseline measurements), Step 3 variable (anxiety sensitivity), Step 4 variable (instructions), Step 5 variable (sequence of inhalation) did not significantly increase the model predictive ability beyond the Step 1 variable. Step 6 variable predicted an additional 14.9% of unique variance (adjusted $R_2 = 0.320$, $F(1, 58) = 8.05$, $p = .000$): inhaling CO_2 was associated with higher post-challange VAAS scores.
- VAS-F: the predictor variables collectively explained 28.8% of the overall variance ($F(9, 58) = 5.66$, $p = .000$). Step 1 variable accounted for 9.1% (adjusted $R_2 = 0.084$) of the variance ($F(1, 66) = 13.43$, $p = .000$). Step 2 variable (baseline measurements), Step 3 variable (anxiety sensitivity), Step 4 variable (instructions), and Step 5 variable (sequence of inhalation) did not significantly increase the model predictive ability beyond the Step 1 variable. Step 6 variable predicted an addition 12.5% of unique variance (adjusted $R_2 = 0.237$, $F(1, 58) = 5.66$, $p = .000$): inhaling CO_2 was associated with higher post-challange VAS-F scores.

- VAS-D: the predictor variables collectively explained 45% of the overall variance ($F(9, 58) = 11.47$, $p = .000$). Step 1 variable accounted for 21.7% (adjusted $R_2 = 0.211$) of the variance ($F(1, 66) = 37.205$, $p = .000$). Step 2 variable (baseline measurements), Step 3 variable (anxiety sensitivity), Step 4 variable (instructions), and Step 5 variable (sequence of inhalation) did not significantly increase the model predictive ability beyond the Step 1 variable. Step 6 variable predicted an additional 19.9% of unique variance (adjusted $R_2 = 0.411$, $F(1, 58) = 11.47$, $p = .000$): inhaling CO_2 was associated with higher post-challange VAS-D scores.
- PSL: the predictor variables collectively explained 52.9% of the overall variance ($F(9, 58) = 15.71$, $p = .000$). Step 1 variable accounted for 6.4% (adjusted $R_2 = 0.057$) of the variance ($F(1, 66) = 9.15$, $p = .003$). Step 2 variable (baseline measurements), Step 3 variable (anxiety sensitivity), and Step 4 variable (instructions) did not significantly increase the model predictive ability beyond the Step 1 variable. Step 5 variable predicted an additional 3.9% of unique variance (adjusted $R_2 = 0.087$, $F(8, 59) = 2.61$, $p = 0.011$): the second gas inhalation was associated with lower post-challenge PSL score. Step 6 variable predicted an addition 38.8% of unique variance (adjusted $R_2 = 0.495$, $F(1, 66) = 15.71$, $p = .000$): inhaling CO_2 was associated with higher post-challange PSL scores.

In table 19 the results of hierarchical multiple regression for physiological measures are presented.

- Systolic blood pressure: the predictor variables collectively explained 58.7% of the overall variance ($F(9, 58) = 19.93$, $p = .000$). Step 1 variable accounted for 54.6% (adjusted $R_2 = 0.542$) of the variance ($F(1, 66) = 160.95$, $p = .000$). Step 2 variable (baseline measurements), Step 3 variable (anxiety sensitivity), Step 4 variable (instructions), and Step 5 variable (sequence of inhalation) did not significantly increase the model predictive ability beyond the Step 1 variable. Step 6 variable predicted an additional 1.9% of unique variance (adjusted $R_2 = 0.548$, $F(1, 66) = 19.93$, $p = .000$): inhaling CO_2 was associated with higher post-challange systolic blood pressure.

Table 18. Hierarchical multiple regression results for psychological variables predicting anxiety response

Predictor	Outcome											
	Post-test VAAS			Post-test VAS-F			Post-test VAS-D			Post-test PSL		
	ΔR^2	B	*SE*	ΔR^2	B	*SE*	ΔR^2	B	*SE*	ΔR^2	B	*SE*
1° Step	**0.174****			**0.091****			**0.217****			**0.064****		
Pre-test score		**13.125****	2.148		**12.252****	1.808		**12.115****	2.171		3.764	0.503
2° Step	0.025			0.027			0.023			0.028		
IAS		0.392	0.199		0.185	0.194		0.104	0.216		0.077	0.048
BAI		-0.450	0.487		0.449	0.482		0.670	0.527		0.057	0.129
BDI		-0.166	0.585		-0.661	0.563		-1.020	0.630		0.009	0.140
STAI-1		-0.070	0.235		0.132	0.228		0.060	0.254		-0.045	0.057
3° Step	0.014			0.018			0.006			0.005		
Anxiety sensitivity		-6.564	4.362		-6.904	4.211		-4.659	4.720		-0.887	1.082
4° Step	0.003			0.013			0.000			0.005		
Instructions		-2.507	3.565		-4.761	3.436		0.348	3.875		-0.744	0.871
5° Step	0.000			0.014			0.006			**0.039****		
Sequence of inhalation		-317	3.562		-4.706	3.228		-3.700	3.762		**-1.964****	0.813
6° Step	**0.149****			**0.125****			**0.199****			**0.388****		
Gas mixture		**16.710****	3.072		**14.157****	3.010		**21.449****	3.174		**6.179****	0.607
Total R^2	**0.365****			**0.288****			**0.450****			**0.529****		

Note. IAS= Illness Attitude Scales; BAI= Beck Anxiety Inventory; BDI= Beck Depression Inventory; STAI-1= State Trait Anxiety Inventory - State; VAAS= Visual Analogue Scale of Anxiety; VAS-F= Visual Analogue Scale of Fear; VAS-D= Visual Analogue Scale of Discomfort; PSL= Panic Symptom List.
**$p \leq 0.01$; *$p \leq 0.05$

Table 19. Hierarchical multiple regression results for physiological variables predicting anxiety response

Predictor	Outcome								
	Post-test Systolic blood pressure			Post-test Diastolic blood pressure			Post-test Heart rate		
	ΔR^2	B	*SE*	ΔR^2	B	*SE*	ΔR^2	B	*SE*
1° Step	**0.546****			**0.565****			**0.656****		
Pre-test score		**49.641****	6.338		**0.913****	0.069		**0.823****	0.051
2° Step	0.013			0.002			0.001		
IAS		-0.192	0.107		-0.032	0.068		0.022	0.074
BAI		0.064	0.259		-0.003	0.166		-0.041	0.183
BDI		0.255	0.316		-0.063	0.197		0.022	0.217
STAI-1		-0.004	0.127		0.057	0.080		0.030	0.088
3° Step	0.002			0.002			0.003		
Anxiety sensitivity		1.973	2.396		-1.073	1.516		1.777	1.639
4° Step	0.006			0.006			0.013		
Instructions		2.528	1.915		-0.924	1.232		2.948	1.321
5° Step	0.001			0.000			0.000		
Sequence of inhalation		-1.202	1.815		-0.211	1.153		-0.069	1.247
6° Step	**0.019***			0.003			0.000		
Gas mixture		**4.275***	1.788		-0.087	1.162		0.053	1.259
Total R^2		**0.587****			0.548			0.673	

Note. IAS= Illness Attitude Scales; BAI= Beck Anxiety Inventory; BDI= Beck Depression Inventory; STAI-1= State Trait Anxiety Inventory - State.
**$p \leq 0.01$; *$p \leq 0.05$

Chapter 4. Discussion

The aim of the present research was to replicate Telch and colleagues study (2011) in the effort to overcome their methodological limitation and investigate the independent and combined effects of anxiety sensitivity (AS) and expectancies on the response to a double inhalation of 35% CO_2 air mixture. We found that the sample showed a greater psychological response and increased systolic blood pressure under CO_2 challenge compared to room air inhalation. However, the psychological and physiological response to the test was not affected by the level of AS (low AS *versus* high AS) or the instructional set (Expected Arousal *versus* Expected Relaxation).

At baseline, as expected high AS group showed significant higher score for ASI-3 (total and subscales) than low AS. Similarly to Telch and colleagues (2011), HAS group had higher scores for baseline affective measures (i.e., BAI, BDI, STAI) compared to LAS group, confirming the association among high AS, depressive symptomatology (Otto et al., 1995), trait anxiety (McWilliams & Cox, 2001), and state anxiety (Sturges, Goetsch, Ridley, & Whittal, 1998). In the present study, IAS and SSAS were also administered at the baseline. Results showed a heightened hypochondriacal concern in HAS group compared to LAS, whereas no differences were found for somatosensory amplification. Concerning the IAS, our result is consistent with previous findings showing that abnormal illness behaviour was associated with AS in a non-clinical sample (Cox, Fuentes, Borger, & Taylor, 2001$_b$; Stewart & Watt, 2000). Even though few studies investigated the relationship between somatosensory amplification and AS, our result is in line with research showing a weak association between SSAS and non-pathological anxiety (Aronson, Barret, & Quigley, 2001; Watt & Stewart, 2000).

At the pre-test HAS group showed a heightened PSL score compared to LAS suggesting the presence of anticipatory anxiety and greater panic symptoms in subjects with high AS compared to

LAS group (Olatunji & Wolitzky-Taylor, 2009). At post-test, HAS and LAS groups did not show significant differences for psychological and physiological response to the CO_2 mixture and room air inhalation. Similarly, no differences were found stratifying the sample for the instructions set.

Thus, to understand the amount of difference between psychological and physiological responses from pre- to post-test, we compared delta scores of the whole sample. Data showed a significant increase in anxiety, fear, discomfort, and panic-like symptoms when CO_2 was inhaled compared to room air. Our result is consistent with the existing literature as well as with Telch and colleagues (2011) which showed that the inhalation of high concentrations of CO_2 produces rapid anxiety and panic-like symptoms (Verburg et al., 2001). According to Fluharty et al. (2016), the inhalation of CO_2, if compared to room air, did not account for changes in physiological parameters. Taking into account the level of anxiety sensitivity, HAS and LAS group showed higher subjective anxiety, fear, discomfort, and panic symptoms under CO_2 inhalation compared to room air, confirming the aforementioned result. However, HAS group presented a significant increase in systolic blood pressure under CO_2 challenge, whereas LAS did not. Accordingly to Reiss and McNally (1985), high AS subjects showed a greater autonomic reactivity (i.e., *enhanced reactivity hypothesis*) in response to stress, thus they developed concerns about arousal-related bodily sensations.

Comparing the response of HAS *versus* LAS group per type of gas inhaled, LAS group showed higher subjective fear in response to room air if compared to HAS. This unexpected result is related to the higher subjective fear of HAS group at pre-test. In fact, negative delta VAS-F score of HAS group indicated a higher level of fear before the inhalation compared to post-test, suggesting an heightened anticipatory anxiety in HAS if compared to LAS group. Our result is not consistent with Telch et al. (2011), who found that HAS group had higher subjective fear at post-test compared to LAS, even after adjusting for baseline affect. A possible explanation is related to the methodological choices made by Telch et al. (2011). They pre-selected subjects scoring at the

extreme level of ASI-3 (i.e., very high *versus* very low AS) whereas, in the present study, we did not preselect in order to have a more representative samples of the population. No statistically significant differences were observed for VAAS, VAS-D, PSL, and physiological parameters under CO_2 challenge and room air. Indeed, taking into account the instructions received and comparing psychological and physiological responses to the challenge, both groups had a higher subjective anxiety, fear, discomfort, and panic symptoms under CO_2 challenge compared to room air. No statistically significant differences were found for blood pressure and heart rate. Our results is consistent with previous findings showing that inhalation of high concentration of CO_2 provoked acute anxiety compared to room air, however not affecting physiological responses (Fluharty et al., 2016).

When we compared the psychological and physiological responses of EA group *versus* ER group, no statistically significant differences were observed. Thus, our results do not support Telch and colleagues (2011) study, who found that the perception of unexpectedness (i.e., ER instructions provided a strong disconfirmation of their expectation under CO_2 inhalation) contribute to heightened subjective anxiety in response to the challenge. Conversely, the present results are consistent with previous studies that showed that instruction manipulation did not affect the rates of panic in non-clinical sample as well as in panic patients (Papp et al., 1995; Welkowitz et al., 1999).

Finally, we investigated the combined effect of AS (high AS *versus* low AS), instructions manipulation (EA instructions *versus* ER instructions), sequence of inhalation (first *versus* second inhalation), and gas type (CO_2 *versus* room air) on emotional responding. Results showed a significant effect of CO_2 challenge on VAAS, VAS-F, VAS-D, PSL, and systolic blood pressure. In addition, a significant effect of the sequence of inhalation on PSL score was found. Indeed, at the second inhalation, subjects reported a statistically significant lower reaction to the challenge if compared to the first inhalation. Evidence for our results comes from studies showing that healthy subjects with high level of AS, who underwent repeated inhalation of CO_2 challenge (i.e., 20% and

35%), presented a decline in anxiety responses across trials, reflecting habituation of anticipatory anxiety (Beck, Shipherd, & Read, 1999; Beck & Wolf, 2001).

Some limitations of this replication study deserve mention. First, the majority of the sample were university students, thereby limiting the external validity of our research although the sample enrolled by Telch and colleagues (2011) was exclusively composed by undergraduate students. Second, physiological parameters were measured immediately before and after each inhalation, rather than continuously; this may have led to the loss of information regarding the emotional responses to the challenge.

Strengths of our study can be found in more strict exclusion criteria (i.e., current organic disease, diagnosis of current psychiatric disorders, family history of panic, current or lifetime history of panic attacks) that have limited the influence of third variables on emotional responding toward the challenge; the measurement of blood pressure, as an additional physiological parameter in response to the challenge; the latest version of ASI-3, that provided better psychometric properties than the previous versions; the methodological choice of matching subjects having a difference of at least one standard deviation at the ASI-3 total score rather than pre-selected subjects with the highest and lowest score at the ASI, solving the problem of heavy-tailed distribution; the methodological choice of double inhalation, which has been shown to provide greater response than the single inhalation of 35% CO_2 in healthy subjects (Nardi et al., 2006; Rassovsky & Kushner, 2003).

Chapter 5. Conclusion

In conclusion, our study confirmed the psychological and physiological effects of 35% CO_2 - 65% oxygen challenge on emotional responses of healthy subjects and suggested that anxiety sensitivity and expectations, evaluated in their independent and combined effect, did not affect the emotional responses. The results strengthen the validity of the 35% CO_2 challenge as well as the goodness of the current standardized instructions used to administer it (Verburg et al., 1998). Indeed, such instructions mention the word “anxiety” (and not the word “panic”) to inform the subjects who accept to undergo the test.

However, further replication studies on this topic are encouraged. It would be interesting to evaluate sample on adults in order to increase the external validity of the research and to include the measurement of cognitive bias in order to investigate whether variables different from anxiety sensitivity or expectations might influence the responses to CO_2 challenge. Indeed, it is noteworthy that our regression analysis explained that only 32.3% and 45.2% of the response to the challenge was due to the mixture and pre-test level of anxiety, and panic symptoms, respectively.

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