35% CO2 sensitivity in social anxiety disorder

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Abstract

The 35% carbon dioxide (CO₂) challenge is a well-established model of panic. This study aimed to investigate 35% CO₂ sensitivity in patients with social anxiety disorder (SAD) compared with patients with panic disorder (PD) and normal controls. First, a 35% CO₂ challenge was conducted including 16 patients with generalized SAD, 16 with PD and 16 normal subjects. Outcome was assessed by a Visual Analogue Scale for Fear (VAS-F) and the Panic Symptom List (PSL). Second, meta-analyses of fear and panic scores were performed, including data from the present experiment and from previous 35% CO₂ challenge studies in patients with SAD. The present 35% CO₂ challenge found equal increases in VAS-F and PSL in patients with SAD compared with normal controls, whereas the CO₂ response in patients with PD was significantly stronger than in controls. The meta-analyses confirmed the experimental data from this study, and in addition showed an intermediate panic rate in SAD patients, in between that of normal controls and patients with PD. In conclusion, neither our experiment nor the meta-analyses found evidence for a similarly exaggerated 35% CO₂ sensitivity in SAD and PD, suggesting that the pathogenesis of SAD is different from PD, although patients with SAD may be slightly more sensitive than non-anxious controls.

Keywords

Biological challenge, carbon dioxide, fear, meta-analysis, panic attack, panic disorder, social anxiety disorder

Introduction

According to the DSM-IV (American Psychiatric Association, 2000), panic attacks can occur in the context of several mental disorders (Reed and Wittchen, 1998). They are the main feature in panic disorder (PD): individuals with PD experience recurrent, unexpected and unpredictable panic attacks, which consequently are the cause of a persistent concern. Symptomatically similar episodes, however, also occur in the context of social anxiety disorder (SAD) (Reed and Wittchen, 1998). The core feature of SAD is fear of acting in an embarrassing or humiliating way, but patients with this condition may also experience panic attacks in certain circumstances. Whereas at least some panic attacks in PD are ‘out of the blue’ and originally not anticipated or connected to certain situations, panic attacks in SAD are specifically linked to social situations (Gelernter et al., 1992). Although the situationally bound panic attacks in SAD phenomenologically resemble the unexpected panic attacks experienced by patients with PD, it is not known if they originate from a common biological mechanism.

The 35% carbon dioxide (CO₂) challenge is a well-established experimental model of panic (Griez and Schruers, 1998, 2003; Rassovsky and Kushner, 2003). In the past, 35% CO₂ hypersensitivity was conceptualized as a specific marker for PD. However, experimental research has shown that CO₂ inhalation elicits panic not only in PD, but also in other nosological entities, such as situational phobias (Verburg et al., 1994). Even healthy subjects have been shown to be sensitive to CO₂ inhalation, in a dose-dependent fashion (Griez et al., 2007). These findings suggest that the CO₂ response may be based on an inborn human survival mechanism, and that CO₂ hypersensitivity is not a simple marker of a single nosological entity. Rather, a continuum of CO₂ sensitivity may exist, in which an increasing degree of sensitivity is related to an

increased vulnerability to panic. The notion of an inborn mechanism is supported by recent neurobiological experiments showing the existence of CO₂/pH-sensitive chemosensors in the brain stem (Hodges and Richerson, 2010; Richerson, 2004) and even in the amygdala (Ziemann et al., 2009), which are known to coordinate fear responses to a variety of threats (Graeff and Del-Ben, 2008; LeDoux, 2000). In this perspective, panic attacks may be viewed as a defensive response to acute and potentially threatening acid–base scenarios (Esquivel et al., 2010), and aberrant chemosensation may underlie anxiety disorders associated with panic attacks (Maren, 2009). For the most part, 35% CO₂ challenges have been conducted in patients with PD, who have consistently been shown to have an exaggerated sensitivity (Fyer et al., 1987; Griez et al., 1987, 1990). Three studies have addressed the issue of the sensitivity of patients with SAD to a 35% CO₂ challenge (Caldirola et al., 1997; Gorman et al., 1990; Papp et al., 1993). The first study, by Gorman and colleagues, aimed at differentiating patients with PD from controls and from another group of patients with anxiety disorder (22 patients with SAD) (Gorman et al., 1990). With reference to this stated purpose the study was negative, as in

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this particular experiment no clear-cut difference was found between the different diagnostic groups. A subsequent study from the same group found intermediate panic rates in patients with SAD (30%), suggesting they are less sensitive than patients with PD (panic rate: 72%), but more than normal controls (panic rate: 4%) (Papp et al., 1993). The most recent 35% CO₂ study found comparable panicogenic reactions in SAD and PD (Caldirola et al., 1997). This CO₂ challenge induced panic attacks in 11 out of 16 PD patients (69%), nine out of 16 SAD patients (56%), seven out of 13 patients with comorbid PD and SAD (54%), three out of seven SAD patients with sporadic unexpected panic attacks (43%) and one out of 16 normal controls (6%). Interestingly, this latest study reported that patients with SAD experienced the CO₂-induced panic attacks as different from anxiety induced by social situations. In conclusion, the current CO₂ challenges apparently do not yield consistent responses in patients with SAD. It remains unclear if CO₂ hypersensitivity plays a role in the pathogenesis of SAD.

The aim of the present study was to investigate CO₂ sensitivity in patients with SAD by two means. First, a 35% CO₂ experiment was performed to compare sensitivity in patients with SAD who had never experienced a spontaneous panic attack, with healthy controls and with patients with PD. Second, meta-analyses including data from the previous CO₂ challenges were conducted to specify the magnitude of differences in CO₂ sensitivity between SAD, PD and normal. Based on the assumption that the pathogenesis of spontaneous panic attacks, which are characteristic for PD, differs from the pathogenesis of situational panic attacks, which also occur in SAD, we hypothesized that patients with SAD would be less hypersensitive to CO₂ than patients with PD.

Methods

35% CO₂ challenge

Subjects. Sixteen patients with SAD, generalized type, and 16 with PD were recruited from the outpatient population of the Academic Anxiety Centre in Maastricht, The Netherlands. Patients were diagnosed according to the DSM-IV criteria and confirmed with the Mini International Neuropsychiatric Interview (Schruiers et al., 2000; Sheehan et al., 1998). The patients with SAD had no comorbid PD and vice versa. Furthermore, the included patients with SAD did not have a history of spontaneous, 'out of the blue' panic attacks. Patients with another primary (i.e. most severe) Axis I or Axis II disorder were excluded. Sixteen healthy controls (NC) were recruited from the general population via advertisement. All subjects gave their informed consent for the procedure after full explanation by the investigators. At the time of testing, all subjects had been free of any use of psychotropic medication, including benzodiazepines, for at least 2 weeks.

Procedure and assessments. The SAD and PD patients completed the Spielberger State and Trait Anxiety inventory (STAI) (Spielberger, 1983) and the Fear Questionnaire (FQ) (Marks and Mathews, 1979) at screening (approximately 1 month before the challenge). The STAI is a 40-item instrument which includes state (STAI-1) and trait (STAI-2) scales, measuring, respectively, transient and enduring levels of anxiety. The FQ is a 15-item

inventory assessing severity of avoidance related to agoraphobic, social and blood-injury fears (Marks and Mathews, 1979).

All participants inhaled a mixture of 35% CO₂ and 65% O₂. Before and after inhalation, subjects filled out a Visual Analogue Scale for Fear (VAS-F) (Schruiers et al., 2011) and the Panic Symptom List (PSL) (Schruiers et al., 2000). The VAS-F was used to measure subjective fear; the range of scores was 0–100, with 0 = no fear and 100 = worst fear imaginable. This instrument has been validated previously for use during 35% CO₂ challenges (van Duinen et al., 2008). The PSL (PSL-IV) was used to evaluate panic symptomatology. It consists of a questionnaire listing 13 items, each item representing a DSM-IV panic symptom, to be rated on a five-point scale, from 0 (absent) to 4 (very intense). The PSL and VAS-F were administered 1 min before and after each inhalation. Δ VAS-F and Δ PSL (post-test scores minus pre-test scores) were calculated for each assessment. Criteria for a panic attack were a rise of at least 25 points on the VAS-F plus an increase in panic symptomatology (Pols et al., 1996; Schruiers et al., 2000).

Data analysis. The present challenge results were analysed as follows. Independent-samples *t*-tests were conducted to compare baseline STAI and FQ scores in SAD and PD. Baseline VAS-F and PSL and the Δ VAS-F and Δ PSL scores were analysed by using analyses of variance (ANOVAs) with one between-group factor (SAD vs. PD vs. NC). Post-hoc comparisons using the Tukey procedure were performed to find out which groups were significantly different from one another. Whenever assumptions for parametric tests (i.e. normal distribution, homogeneity of variance) were not met, non-parametric alternatives were used (Kruskal–Wallis Test, Mann–Whitney *U* Test). The number of panic attacks following the CO₂ challenge was calculated for each group and compared with chi-square tests.

Meta-analyses

Meta-analyses were conducted to quantitatively specify the magnitude of group differences in 35% CO₂ sensitivity between SAD patients, PD patients and normal controls. To the best of the authors' knowledge, all English-written published 35% CO₂ challenges up to 1 January 2011 that included patients with SAD were reviewed. Whenever anxiety and panic responses to CO₂ of patients with SAD were obtainable directly from the articles, effect sizes of these measures were calculated and included for meta-analyses. In particular, within each study, the standardized mean change (Gibbons et al., 1993) for each group was computed (i.e. $d = (\bar{x}_{post} - \bar{x}_{pre})/SD_D$, where $\bar{x}_{pre}$ and $\bar{x}_{post}$ are the means on the anxiety or panic outcome measure before and after the CO₂ challenge and SD_D denotes the standard deviation of the change scores). Standardization was necessary, since the instruments to assess anxiety and panic responses differed across studies. Based on the information provided in the articles, the proportion of cases in the three groups that experienced a panic attack (i.e. the panic rate) was also determined. Then, three separate meta-analyses were conducted using random-effects models to aggregate the anxiety and panic effect sizes and the panic rates across studies and to compare them across groups (for details on the model

used, see Salanti et al., 2008). A constant heterogeneity across the three group contrasts (i.e. SAD vs. NC, PD vs. NC, and SAD vs. PD) was assumed. The models were fitted using restricted maximum likelihood estimation. Results are presented in terms of the estimated mean d values ($\bar{d}$) or mean panic rates ($\bar{p}$) of the three groups (with corresponding 95% confidence intervals) based on the random-effects models. If the omnibus test of equal effects (or rates) across the three groups was rejected, the pairwise contrasts (e.g. $\bar{d}_{PD} - \bar{d}_{NC}$) were also examined. In addition, forest plots are presented, showing the individual and aggregated d values and panic rates. Likelihood ratio tests were used to test whether the amount of heterogeneity in the data was significantly larger than 0.

Results

35% CO₂ challenge

There were six men (37.5%) and 10 women (62.5%) in each of the three groups. There were no significant differences between the groups in mean age (SAD: 32.8 ± 10.0 years; PD: 32.8 ± 9.5 years; NC: 30.2 ± 10.2 years; $F(2,45) = 0.4$, $p = 0.7$). Mean scores on STAI 1, STAI 2 and FQ-SP (see Table 1) were significantly higher in the SAD group compared with the PD group ($t(29) = -3.5$, $p = 0.001$, $t(28) = -6.0$, $p < 0.001$ and $t(29) = -6.4$, $p < 0.001$, respectively). The groups differed in baseline score on the VAS-F (Kruskal–Wallis $\chi^2 = 12.3$, $df = 2$, $p < 0.01$), with significantly higher scores in the SAD group and PD group compared with the NC group ($z = -2.6$, $p < 0.01$ and $z = -3.4$, $p < 0.001$, respectively). Similar differences were found in baseline PSL scores (Kruskal–Wallis $\chi^2 = 15.3$, $df = 2$, $p < 0.001$): the anxiety groups showed significant higher scores than the NC group ($z = -2.4$, $p < 0.02$ for SAD and $z = -3.8$, $p < 0.001$ for PD). Mean scores are presented in Table 1.

Δ VAS-F. A one-way ANOVA revealed a significant difference in Δ VAS-F across the three groups ($F(2,45) = 6.1$, $p < 0.005$). Post-hoc comparisons using the Tukey procedure showed significant differences with higher scores in the PD group when compared with the NC ($p < 0.005$) and when compared with the SAD ($p < 0.05$) group. The SAD group did not differ significantly from the NC group ($p = 0.66$). A graphical reproduction is shown in Figure 1.

Δ PSL. There was a significant difference in Δ PSL for the three groups ($F(2,45) = 4.2$, $p = 0.02$). Post-hoc comparisons showed a significant difference between PD and NC ($p < 0.02$), with a higher mean score for the PD group (Table 1). The SAD group did not differ significantly from the NC group, nor from the PD group ($p = 0.20$ and $p = 0.50$ respectively). See Figure 1 for a graphical reproduction.

Panic rate. There were 12 panic attacks in the PD group, eight in the SAD group and three in the NC group. A 2×3 chi-square analysis revealed a significant difference in the number of panic attacks among the three groups ($\chi^2 = 10.2$, $p = 0.006$). Post-hoc comparisons showed that the panic rate in the PD group was

significantly higher than in the NC group ($\chi^2 = 10.2$, $p < 0.002$). patients with SAD did not differ significantly from patients with PD ($\chi^2 = 2.1$, $p = 0.14$), nor from the NC group ($\chi^2 = 3.5$, $p = 0.06$).

Meta-analysis

Included studies. In addition to our CO₂ study presented in this article, three previous 35% CO₂ challenges were identified as eligible for inclusion in the current meta-analyses (Caldirola et al., 1997; Gorman et al., 1990; Papp et al., 1993).

Table 1. Mean ($\pm$ SD) scores for 16 patients with Social Anxiety Disorder (SAD), 16 patients with Panic Disorder (PD) and 16 Normal Controls (NC)

	SAD	PD	NC
STAI 1	49.4 ($\pm$ 10.1)*	36.6 ($\pm$ 10.0)	-
STAI 2	58.5 ($\pm$ 11.5)**	37.7 ($\pm$ 7.4)	-
FQ-A	13.1 ($\pm$ 13.8)*	14.6 ($\pm$ 12.3)	-
FQ-SP	26.1 ($\pm$ 9.6)*	7.6 ($\pm$ 6.1)	-
FQ-BI	12 ($\pm$ 10.4)*	10 ($\pm$ 6.7)	-
VAS-F			
Before inhalation	21.4 ($\pm$ 24.6)	18.8 ($\pm$ 17.0)	2.1 ($\pm$ 2.8)
After inhalation	44.0 ($\pm$ 34.4)	67.1 ($\pm$ 21.3)	15.8 ($\pm$ 22.7)
Increase	22.6 ($\pm$ 36.1)	48.4 ($\pm$ 27.4)	13.7 ($\pm$ 22.4)
PSL			
Before inhalation	3.0 ($\pm$ 5.0)	4.0 ($\pm$ 3.2)	0.5 ($\pm$ 0.8)
After inhalation	13.5 ($\pm$ 9.2)	17.2 ($\pm$ 9.1)	6.4 ($\pm$ 4.3)
Increase	10.5 ($\pm$ 9.4)	13.4 ($\pm$ 7.6)	5.9 ($\pm$ 3.9)

STAI, State (1)-Trait (2) Anxiety Inventory; FQ, Fear Questionnaire; -A, Agoraphobia; -SP, Social Phobia; -BI, Blood Injury; VAS-F, Visual Analogue Scale for Fear; PSL, Panic Symptom List. * $n = 15$; ** $n = 14$.

Figure 1. Mean (standard error) Δ VAS-F and Δ PSL scores for 16 patients with Panic Disorder (PD), 16 patients with Social Anxiety Disorder (SAD) and 16 Normal Controls (NC).

Except for the study of Gorman et al. (1990), which used double-breath, all studies employed the single-breath inhalation method. All studies assessed CO₂ response by means of a fear scale, a panic symptom scale and all defined criteria for a panic attack. The American studies (Gorman et al., 1990; Papp et al., 1993) used a 10-point scale for assessing fear and the 28-item Acute Panic Inventory (Dillon et al., 1987), whereas the Italian group (Caldirola et al., 1997) used the same scales as we did in the present CO₂ study (i.e. VAS and PSL). Unfortunately, the latter study did not provide data on absolute mean changes in VAS and PSL and therefore could not be included in meta-analyses of changes in fear and panic symptomatology. Panic attacks were defined differently in the four studies, but the definitions all included a combination of increase in fear and in panic symptomatology. All studies used self-ratings for defining a panic attack, with the exception of Gorman et al. (1990), which asked an attending psychiatrist to judge whether an actual panic attack occurred.

The characteristics of the subject groups of the included studies are shown in Table 2. The subjects in the Italian study were slightly younger, and there was a preponderance of men in the SAD groups of the American studies.

Effect sizes. Figure 2 depicts the forest plot of the standardized mean changes in fear response to CO₂ inhalation in control, SAD and PD groups. The random-effects model indicated that the largest increases in fear occurred in the PD group ($\bar{d} = 1.10$, 95% CI: 0.77–1.43), followed by the SAD ($\bar{d} = 0.79$, 95% CI: 0.50–1.09)

and control groups ($\bar{d} = 0.59$, 95% CI: 0.30–0.88), the latter showing the lowest increases. The differences in the standardized mean changes between the three groups were significant ($\chi^2 = 6.1$,

Table 2. Characteristics of the Subject Groups in included studies

Groups	Study	N	Age (Mean $\pm$ SD, y)	Sex (% Male)
Control groups				
	Gorman et al., 1990	14	27.1 $\pm$ 5.6	50
	Papp et al., 1993	23	31.2 $\pm$ 8.6	61
	Caldirola et al., 1997	16	25.8 $\pm$ 2.8	69
	Schutters et al., 2011 (current study)	16	30.2 $\pm$ 10.2	37
Social anxiety disorder groups				
	Gorman et al., 1990	22	34.9 $\pm$ 8.5	64
	Papp et al., 1993	20	34.3 $\pm$ 9.2	80
	Caldirola et al., 1997	16	30.7 $\pm$ 9.6	37
	Schutters et al., 2011 (current study)	16	32.8 $\pm$ 10.0	37
Panic disorder groups				
	Gorman et al., 1990	26	34.7 $\pm$ 8.2	38
	Papp et al., 1993	18	35.3 $\pm$ 9.6	33
	Caldirola et al., 1997	16	31.7 $\pm$ 6.4	50
	Schutters et al., 2011 (current study)	16	32.8 $\pm$ 9.5	37

Figure 2. Forest plot of the standardized mean change in fear.

$df = 2$, $p = 0.047$). The PD group had a significantly higher increase than the control group ($\bar{d}_{PD} - \bar{d}_{NC} = 0.57$, $p = 0.01$). Patients with SAD differed significantly neither from controls ($\bar{d}_{SAD} - \bar{d}_{NC} = 0.23$, $p = 0.29$), nor from patients with PD ($\bar{d}_{PD} - \bar{d}_{SAD} = 0.34$, $p = 0.13$). All of the heterogeneity in the data could be accounted for based on sampling variability.

Figure 3 displays the forest plot of the standardized mean changes in panic symptomatology in response to CO₂ inhalation in control, SAD and PD groups. The random-effects model indicated the highest increases in the PD ($\bar{d} = 1.24$, 95% CI: 0.90–1.58), followed by control ($\bar{d} = 1.01$, 95% CI: 0.68–1.35) and SAD ($\bar{d} = 0.96$, 95% CI: 0.65–1.27) groups. However, the differences between the three groups was not significant ($\chi^2 = 1.9$, $df = 2$, $p = 0.39$). No heterogeneity was again found in the data.

The forest plot for the panic rates is shown in Figure 4. The differences in the rates between the control, SAD and PD groups were significant ($\chi^2 = 69.9$, $df = 2$, $p < 0.0001$). The risk of patients with SAD experiencing a panic attack during the CO₂ challenge was $\bar{p} = 0.41$ (95% CI: 0.30–0.53), falling in between the panic rate of controls ($\bar{p} = 0.09$, 95% CI: 0.01–0.17) and PD groups ($\bar{p} = 0.66$, 95% CI: 0.54–0.77). All pairwise contrasts between the three groups were significant (all $p < 0.001$). Some slight heterogeneity was present in the data, but it was not significant ($p = 0.44$).

Discussion

Both the present 35% CO₂ experiment and the meta-analyses of 35% CO₂ responses showed that patients with SAD do not report more CO₂-induced fear or panic symptomatology than normal controls, whereas patients with PD show significantly higher reactions on all assessment methods used. The differences between SAD and PD were not significant for fear or panic symptom measures, but the meta-analysis found intermediate CO₂-elicited panic rates in SAD, midway between normal and PD. This strongly suggests that SAD patients may react more than controls, but certainly not as strongly as patients with PD.

Therefore, the results are in line with the idea of an intermediate CO₂ reactivity in SAD, as suggested by some earlier studies (Blecher et al., 2010; Holt and Andrews, 1989b; Papp et al., 1993). CO₂ studies in patients with other anxiety disorders and in healthy subjects support a continuum model for CO₂ vulnerability. For instance, patients with obsessive-compulsive disorder and animal phobia react in a way similar to healthy controls (Griez et al., 1990; Perna et al., 1995a; Verburg et al., 1994). On the other hand, patients with situational phobia and healthy subjects with infrequent panic attacks display a CO₂ sensitivity close to that seen in patients with PD (Perna et al., 1995b; Verburg et al., 1994). Further supporting the continuum model is the finding that negative affect in healthy subjects depends on the concentration of CO₂ used (Griez et al., 2007; Schruers et al., 2011).

Figure 3. Forest plot of the standardized mean change in panic symptomatology.

Figure 4. Forest plot of the panic rate.

Since the CO₂ challenge strongly disturbs the 'internal milieu', it is possible that the degree of CO₂ susceptibility may be a function of vulnerability to (threatening) interoceptive cues. Conceivably, there is a spectrum of interoceptive vulnerability within anxiety disorders. Patients with PD appear to be most sensitive for internally generated cues (Craske, 1991). At the other extreme, animal phobia is characterized by a fear of a purely external stimulus, suggesting a high sensitivity for exteroceptive cues (Craske and Sipsas, 1992). The same may apply to obsessive-compulsive disorder, in which, for example, contamination by germs is feared. With regard to SAD, sensitivity to both exteroceptive and interoceptive cues seems to play a role. Patients with SAD are typically afraid of negative evaluation by others. Therefore, they may be most vulnerable for external social cues. Yet, patients with SAD may also be hypersensitive for interoceptive cues, as cognitive models have suggested an important role of heightened self-focus in SAD (Clark and Wells, 1995). Empirical research has in addition found an increased awareness of autonomic anxiety symptoms in patients with SAD, certainly when these symptoms may be obvious to the external world (e.g. sweating, blushing) (Anderson and Hope, 2009; Spector et al., 2003). Several studies found an exaggerated physiological arousal in the non-generalized subtype of SAD (Heimberg et al., 1990; Hofmann et al., 1995; McTeague et al., 2009), suggesting this subtype may resemble PD. Our sample specifically included patients with the generalized SAD, but the subtype was not specified in the

previous 35% CO₂ challenges (Caldirola et al., 1997; Gorman et al., 1990; Papp et al., 1993). It is conceivable that the SAD patients with an exaggerated response to CO₂ are those who predominantly experience autonomic symptoms, such as the non-generalized subtype. The highest CO₂ sensitivity may be found in patients with respiratory symptoms, such as in the respiratory subtype of PD (Freire et al., 2008, 2010), because these symptoms specifically have been shown to be the best predictors for panic in a CO₂ experiment (Colasanti et al., 2008). Further CO₂ studies addressing the type of symptoms (blushing, sweating, palpitations, dyspnoea) induced by the 35% CO₂ challenge are needed to elucidate if CO₂ vulnerability is related to autonomic hyperactivity and respiratory symptoms in SAD.

The present results should be viewed in light of several limitations. First, the sample sizes of the present CO₂ experiment were rather small, therefore the possibility of a Type 2 error cannot be excluded. However, this was the reason for the meta-analyses, which support our experimental results. Second, assessment instruments were those from previous CO₂ studies (VAS and PSL) and these do not include specific social anxiety symptoms. Nevertheless, VAS and PSL have been shown to be reliable tools for investigating biological CO₂ sensitivity (Rassovsky and Kushner, 2003). Finally, it should be acknowledged that the present meta-analyses only addressed the 35% CO₂ challenge. The reason for this were the methodological differences with other challenges (Bleichert et al., 2010; Holt and Andrews, 1989a,

1989b; Rapee et al., 1992). Moreover, one of the 35% CO₂ studies lacked data on CO₂-induced changes in fear and panic symptomatology (Caldirola et al., 1997) and therefore could not be included in the respective meta-analyses.

In conclusion, neither our experiment nor the meta-analyses found evidence for an exaggerated 35% CO₂ sensitivity in SAD as is known in PD. The CO₂-elicited panic rate of patients with SAD appears intermediate, in between PD patients and non-anxious individuals. The results generally suggest that the pathogenesis of SAD is different from PD.

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Conflict of interest

The authors declare that they have no conflict of interest.

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