Are Respiratory Abnormalities Specific for Panic Disorder? A Meta-Analysis

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Key Words

Panic attacks · Social phobia · Anxiety disorders · Affective disorders · Biological psychiatry

Abstract

Objectives: There is evidence of baseline respiratory abnormalities in panic disorder (PD), but whether they are specific to PD remains unclear. To investigate this issue, we meta-analyzed results from studies comparing baseline respiratory and hematic variables between subjects with PD and subjects with other anxiety disorders. **Methods:** A literature search in bibliographic databases was performed. Fixed-effects models were applied. Several moderator analyses and publication bias diagnostics were performed. **Results:** We found: (1) significantly lower mean end-tidal partial pressure of CO₂ (et-pCO₂) in subjects with PD than in those with social phobia (SP) or generalized anxiety disorder (GAD), and (2) higher mean respiratory rate, lower venous et-pCO₂ and HCO₃⁻ concentration in subjects with PD than in those with SP. No publication bias was found. **Conclusions:** Subjects with PD show a condition of baseline hyperventilation when compared to subjects with SP or GAD. Hematic variables suggest that the hyperventilation may be chronic. These results support the idea that baseline respiratory abnormali-

ties are specific to PD pathophysiology. Further studies are needed to clarify whether these abnormalities are related to a malfunction of the respiratory system or to specific cognitive/emotional/behavioral factors in this population.

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Introduction

A link between panic disorder (PD) and respiration is well established. The presence of prominent respiratory symptoms during panic attacks, the behavioral and respiratory hypersensitivity to hypercapnic gas mixture-inhalation in patients with PD, and a specific bidirectional association between PD and respiratory diseases support this link [1, 2]. Several theories sharing the idea of a causal relationship between aberrant respiratory regulation and panic have been developed [2–5], even though the nature of this respiratory abnormality is not yet fully understood.

We recently performed a meta-analysis of studies that compared PD and control groups on baseline respiratory variables and hematic variables related to the respiratory function [6]. We found higher baseline mean minute ventilation (MV), lower end-tidal partial pressure of CO₂

(et-pCO₂) and lower venous pCO₂ in subjects with PD, indicating a condition of baseline hyperventilation. Our results of reduced HCO₃⁻ (bicarbonate ion) and PO₄⁻ (phosphate ion) venous concentrations in these subjects suggest that hyperventilation may be chronic and not simply related to high anxiety levels the subjects may have experienced during the respiratory assessment. Finally, we also found indications of higher variability of MV, respiration rate (RR) and tidal volume (TV), higher RR and TV irregularity, and a higher rate of sighs and apneas in the respiratory patterns of subjects with PD.

Whether these respiratory abnormalities are specific to PD or shared with other anxiety disorders (ADs) remains an open issue. Available studies comparing baseline respiratory variables between subjects with PD and those with other ADs yielded mixed results [7–9] and, to the best of our knowledge, published systematic reviews or meta-analyses are lacking.

The aim of our study was to investigate the specificity of the baseline respiratory abnormalities by meta-analysis of the results from all studies comparing baseline respiratory variables between subjects with PD and subjects with other ADs. To clarify this issue may help to better understand the pathophysiology of PD.

Methods

Inclusion Criteria

We included studies that fulfilled the following criteria: (1) performed a comparison of respiratory and/or hematic variables related to the respiratory function between subjects with PD, with or without agoraphobia, and subjects with other ADs; (2) variables were measured only in a resting or baseline condition preceding a subsequent stimulation (henceforth we will use the term 'baseline' to refer to both conditions); (3) inclusion of the subjects was not based on the results of previously performed challenges or stimulations; (4) subjects were ≥ 18 years of age; (5) criteria of AD diagnoses according to DSM-III [10], DSM-III-R [11] or DSM-IV/DSM-IV-TR [12, 13]; (6) was published in a peer-reviewed scientific journal; (7) enough statistical data had to be available to allow the meta-analytic computation, and (8) written in English, French, Spanish or Italian.

Search Procedure

Literature searches were performed in PubMed, Embase and Psychinfo with this combination of search terms: 'panic* AND (respirat* OR breath* OR hyperventilat* OR (tidal volume) OR (minute ventilation) OR pCO₂ OR pO₂ OR sigh OR sighs)'. Papers from 1980, when the diagnosis of PD was first introduced in DSM-III [10], to December 31, 2013 were searched. References were screened using a two-step procedure: (1) the titles and the abstracts of all the references were read to select all potentially relevant papers, and (2) the full text was read to identify which studies fulfilled

the inclusion criteria. Furthermore, references of all selected papers, relevant reviews and book chapters were screened to find studies potentially missed with the previous search. Each step of the search procedure was independently performed by two of the authors and inconsistencies in the results were discussed and resolved before proceeding.

Effect-size Calculation and Coding of Studies

For all of the included studies, we calculated the baseline respiratory variable effect sizes of comparisons between subjects with PD, with or without agoraphobia, and subjects with other ADs. Effect sizes were calculated using Hedges' *g*, a variation of Cohen's *d*, correcting for biases associated with small sample sizes [14]. When the group mean, standard deviation (SD), variance or standard error of mean and number of subjects were available for both groups, these data were preferably used to calculate the effect size. When some of these data were missing, we looked for other data allowing the effect-size computation, such as unstandardized mean difference as well as *t* and *p* values. When the statistics of the variables were available for only subgroups of the diagnostic groups (i.e. male and female), data of the whole diagnostic groups were obtained by pooling subgroup statistics.

Moreover, the following study characteristics were coded and included in the analyses as moderators: (1) subjects who were medication-free for at least 2 weeks before assessment, except for occasional use of benzodiazepines, and subjects completely refraining from occasional use of benzodiazepines for at least 24 h before the day of the respiratory assessment: yes/no; (2) subjects being screened for medical illnesses and presence of respiratory diseases: yes/no; (3) type of study, i.e. resting/with stimulation; (4) subjects having an inserted catheter during the respiratory assessment: yes/no; (5) the position of the subjects during respiratory assessment: supine or seated, and (6) psychiatric diagnosis performed by structured or semistructured diagnostic interview: yes/no.

Computation of the effect size and coding of the studies were performed independently by two authors and any discrepancy was resolved before analysis.

Meta-Analytic Statistics

In the calculation of the summary effect size of each variable (i.e. the estimate of the population effect size resulting from the meta-analysis), every single-study effect size was weighted by its inverse variance to give a larger weighting to studies with large sample sizes than those with small sample sizes. Before excluding a study for not meeting inclusion criterion 7, we tried to contact the corresponding author (only for studies published not more than 10 years ago) asking for the missing details. When papers did not report enough data for the computation of a nonsignificant effect size and we failed to obtain full details from the authors, we included it inserting a null-effect size in the analysis. In order to increase the reliability of such a procedure, the inclusion was done only if the result of a nonsignificant difference was clearly reported in the paper. Otherwise the comparison was excluded from the analyses; we also excluded studies in which the computation of both significant and nonsignificant effect sizes was not possible (see inclusion criterion 7). Thus, when appropriate, two distinct analyses including and excluding null effect sizes were performed. In order to avoid excessive imprecision of the results, only variables that were explicitly calculated in at least two studies were meta-analyzed.

A fixed-effects model was calculated for all the variables. We also used a random-effects model only when the number of available studies was at least 10 [6]. Concordance of the results obtained by the two meta-analytical models was considered strongly suggestive of reliable results, while we attempted to clarify the significance of the fixed-effects model and nonsignificance of the random-effects model according to results of moderator analysis. Results obtained only by the fixed-effects model were considered preliminary. A significance level of 0.05 was applied to the summary effect sizes.

A Q statistic and I^2 index were used to investigate the heterogeneity of the effect sizes among studies. The significance level of the Q statistic was set at 0.1 as suggested by the authors [15] to adjust for the limited statistical power of this test. I^2 can be interpreted as the percentage of the total variability in a set of effect sizes that cannot be attributed only to the sampling error within studies. If the Q statistic resulted significant or I^2 suggested heterogeneity, we checked whether the source of this heterogeneity might have been attributed to one single effect size outlying from all others. In this case we repeated the meta-analytic analyses one-by-one removing each effect size. An effect size was considered outlying when its exclusion from the analyses yielded to a resolution of the heterogeneity, and its inclusion during the removal of other effect sizes did not. The one-by-one exclusion procedure was not performable when only two single-study effect sizes were available for comparison.

All analyses were performed with Comprehensive Meta-Analysis (version 2.2.048), a statistical analysis package by Biostat Inc.

Moderator Analyses

To find possible sources of heterogeneity among the baseline respiratory variable effect sizes, we also performed moderator analyses with the aforementioned study characteristics. We performed separate fixed-effects models within each level of the moderators and then compared them with the between-groups Q statistic. Statistical significance for moderator analysis was set at $p < 0.05$.

Publication Bias

We performed the Egger's regression test to check for possible publication bias [16] (one-tailed $p < 0.05$ suggesting presence of the bias). We also used the trim-and-fill method from Duval and Tweedie [17] if the summary effect sizes were based on at least 10 studies [18].

Results

Included Studies

The literature search yielded 3,582 unique references.

The first screening step (examination of titles and abstracts) identified 25 references potentially including comparisons of respiratory variables between subjects with PD and those with other ADs. The independent selections were carried out by two of the authors and yielded 23 and 25 references, respectively. The two nonmatching references were included in the total selected refer-

ences to be further reviewed in full-text (second step). Thirteen independent studies reported in 14 different papers fulfilled the inclusion criteria and were finally included in the analysis. Eight papers were excluded because the studies they reported did not satisfy the inclusion criteria. One study was excluded because the baseline respiratory variables were measured during daily-life registration [19], another study was excluded because the baseline assessment period contained a 15-second countdown to the CO₂ challenge that was not excluded from the baseline respiratory variables assessment [20] and one more study was excluded due to an inconsistency in the sample size declared in the paper [21].

All details about the inclusion/exclusion of studies are provided as supplementary data (for all online suppl. material, see www.karger.com/doi/10.1159/000364830) and a flowchart of the general inclusion procedure is reported in figure 1.

Computation of Effect size and Coding of Studies

No reply was received from any author we contacted to obtain missing data. Thus, we excluded these studies or, when possible, inserted null effect sizes in the analyses, as previously described. Descriptions of all the included studies with relevant variables and study-level characteristics coded for each study are reported in table 1.

Since only unique studies were identified that compared subjects suffering from PD with subjects, respectively, suffering from posttraumatic stress disorder, obsessive-compulsive disorder and simple phobia, no meta-analysis was performable for these comparisons.

Comparisons between PD and Social Phobia. Thirty-eight effect sizes of baseline respiratory variables were calculated: 19 by means, SD and group sizes, while 19 null effect sizes were inserted in the analysis. No disagreements on the calculations among the two authors emerged. Only the variables with at least two effect sizes from two independent studies were meta-analyzed, and these were mean RR (breath/min), TV (ml/breath), MV (l/min), et-pCO₂ (mm Hg), venous pCO₂ (mm Hg), HCO₃⁻ (mmol/l) and pH.

Comparisons between PD and Generalized Anxiety Disorder. Thirty-eight effect sizes were calculated: 28 by means, SD and group sizes, while 19 null effect sizes were inserted in the analysis. Disagreements regarding two effect sizes calculated independently by the two authors were unanimously resolved. Only variables that had at least two effect sizes from two independent studies were suitable to be meta-analyzed, i.e. mean RR (breath/min), MV (l/min) and et-pCO₂ (mm Hg).

Fig. 1. Study inclusion flowchart.

Meta-Analytic Results of Baseline Respiratory Variables

Detailed results of analyses are reported in tables 2 and 3. Forest plots are provided as supplementary data. None of the variables meta-analyzed were available in at least 10 studies. Therefore, only fixed-effects models were performed for all the variables.

Comparisons between PD and Social Phobia. All the details are reported in table 2. Baseline mean RR was significantly higher in subjects with PD than in subjects with social phobia (SP), both when including and excluding null-effect sizes, respectively ($h_i = 0.333$; $h_e = 0.473$). Instead, the summary effect sizes of mean TV and MV indicated no significant differences between PD and SP. For the summary effect sizes of the mean et-pCO₂, the comparisons were significant when both including and excluding null effect sizes, indicating lower baseline et-pCO₂ in subjects with PD than with SP ($h_i = -0.283$; $h_e = -0.51$). Summary effect sizes of venous pCO₂ and HCO₃⁻ were significant and indicate lower venous pCO₂ ($h = -0.562$) and lower venous concentrations of HCO₃⁻ ($h = -0.785$) in subjects with PD than in subjects with SP. Instead, the summary effect size estimates for venous pH were not significant.

Evidence of heterogeneity was found for mean TV (excluding null-effect sizes) and venous pH, as indicated by the significant Q statistics, and for mean MV (excluding null-effect sizes) as suggested by I². Since only two independent studies were available, the one-by-one exclusion procedure was not performable.

Comparisons between PD and Generalized Anxiety Disorder. All details are reported in table 3. The summary effect size of mean RR comparisons indicates a signifi-

cantly higher mean RR in subjects with PD than in subjects with GAD ($h_i = 0.259$; $h_e = 0.297$), both when including and excluding null-effect sizes, whereas the summary effect sizes was not significant for mean MV. Summary effect sizes of mean et-pCO₂ were significant, both when including and excluding null-effect sizes, indicating lower et-pCO₂ in subjects with PD than in subjects with generalized anxiety disorder (GAD; $h_i = -0.420$; $h_e = -0.505$).

The significance of Q statistics demonstrated between-study heterogeneity for mean RR and mean et-PCO₂. Analyses identified the mean RR effect size of Munjack et al. [7] as the primary source of heterogeneity in the summary effect size. The exclusion of this study drastically reduced such heterogeneity whereas, by applying the one-by-one exclusion procedure for all the other single-study effect sizes, the Q statistic remained significant. Indeed, the mean RR effect size of Munjack et al. [7] was the lone indication of a significantly higher mean RR in the PD group than in the GAD group, with an effect size extremely large in magnitude ($h = 1.276$). Meta-analysis of the mean RR performed with the exclusion of Munjack et al. [7] did not indicate a significant difference between PD and GAD (table 3). Instead, analyses for mean et-pCO₂ could not identify any particular effect size as the primary source of heterogeneity (detailed results available upon request).

Moderator Analyses. Moderator analyses (i.e. psychotropic medication washout, medical screening, type of study, catheter, position of the subjects during assessment, or structured or semi-structured diagnostic interview) were performed for all variables that showed relevant heterogeneity, except for mean RR comparisons between PD and GAD groups since the one-by-one study

Table 1. Baseline respiratory parameters and coded characteristics and of included studies

Study	Respiratory parameter	Statistic of respiratory parameter	PD compared to	Study type	Subjects' position	Catheter	Psychotropic drug wash-out criteria	Diagnostic interview	Medical screening and no subjects affected by respiratory diseases (PD subjects + controls)
Asmundson and Stein, 1994 [42]	Respiration rate, et-pCO ₂ (mm Hg)	mean	SP	stimulation	seated	no	yes	yes	yes
Asmundson and Stein, 1994 [43]	Et-pCO ₂ (mm Hg)	mean	SP	stimulation	seated	no	no	yes	yes
Blechert et al., 2007 [20]	Et-pCO ₂ (mm Hg); Ribcage contribution to Tidal Volume; rate of sighs (>200% tidal volume)	mean	PTSD	stimulation	seated	no	no	yes	yes
Burkhardt et al., 2010 [34]	Respiration rate, tidal volume, minute ventilation, et-pCO ₂ (mm Hg), duty cycle, inspiration flow	mean	SP	rest	seated	no	no	yes	yes
	Respiration rate, tidal volume, minute ventilation, et-pCO ₂ (mm Hg), duty cycle, inspiration flow	rMSSD							
Gorman et al., 1990 [38]	Respiration rate, tidal volume, minute ventilation	mean	SP	stimulation	seated	yes	yes	no	no
	Venous pCO ₂ , venous HCO ₃ ⁻ , venous pH, venous PO ₄ ⁻	-							
Hegel and Ferguson, 1997 [44]	Respiration rate, et-pCO ₂ (mm Hg)	mean	GAD	stimulation	seated	no	no	yes	yes
Munjack et al., 1993 [7]	Respiration rate, et-pCO ₂ (mm Hg)	mean	GAD	rest	seated	no	no	no	no
Papp et al., 1993 [45]	Respiration rate, tidal volume, minute ventilation	mean	SP	stimulation	supine	yes	yes	no	yes
	Venous pCO ₂ , venous HCO ₃ ⁻ , venous pH	-							
Rapee, 1986 [35]	Minute ventilation, et-pCO ₂ (mm Hg)	mean	GAD	stimulation	seated	no	no	no	yes
Rapee et al., 1992 [46]	Respiration rate, et-pCO ₂ (mm Hg)	mean	GAD, SP, OCD, SimpP	stimulation	seated	no	no	yes	yes
Roth et al., 1998 [37]	Respiration rate, tidal volume, minute ventilation, et-pCO ₂ (mm Hg), duty cycle, inspiration flow, length of inspiration, pause after inspiration, length of expiration, pause after expiration	mean	GAD	stimulation	seated	no	yes	yes	yes
Wilhelm et al., 2001 [9]	Respiration rate, tidal volume, minute ventilation, et-pCO ₂ (mm Hg), duty cycle, inspiration flow	mean	SP	stimulation	seated	no	yes	yes	no
	Respiration rate, tidal volume	complex demodulation							
Wilhelm et al., 2001 [8, 47]	Respiration rate, tidal volume, tidal volume – sighs removed, minute ventilation, et-pCO ₂ (mm Hg), rate of apneas (>5 s), duty cycle, inspiratory drive, length of sighs (>200% tidal volume; n°/min)	mean	GAD	rest	seated	no	yes	yes	yes
	Respiratory rate, tidal volume	mean							
	Tidal volume	SD							
	Respiration rate, tidal volume, tidal volume – sighs removed, minute ventilation, et-pCO ₂ (mm Hg), duty cycle, inspiratory drive	rMSSD							
	Respiration rate, tidal volume, tidal volume – sighs removed, minute ventilation, et-pCO ₂ (mm Hg), duty cycle, inspiratory drive	complex demodulation							
	Rate of sighs (>200% tidal volume)	-							

The value indicated in the columns 'Psychotropic drug wash-out (weeks)' and 'Occasional use of benzodiazepine suspension (days)' refer to the subjects with minimum period of suspension; n.a. = information not available; n.t. = not under treatment; PTSD = post-traumatic stress disorder; OCD = Obsessive Compulsive Disorder; SimpP = Simple Phobia; rMSSD = root mean square of the successive differences.

Table 2. Meta-analysis comparisons between PD and SP groups

Baseline respiratory parameters	Studies, n	PD, n	SP, n	Fixed-effects model				Heterogeneity		
				g	95% CI	Z	p	Q	p	I ²
<i>Mean</i>										
RR (breath/min)										
Including null e-s	6	148	128	0.333	0.092 to 0.575	2.704	0.007*	5.157	0.397	3.038
Excluding null e-s	4	114	85	0.473	0.185 to 0.761	3.220	0.001*	2.100	0.552	0.000
TV (ml/breath)										
Including null e-s	4	54	70	0.035	−0.316 to 0.386	0.194	0.846	4.236	0.237	29.182
Excluding null e-s	2	20	27	0.092	−0.480 to 0.664	0.317	0.752	4.174	0.041*	76.041
MV (l/min)										
Including null e-s	4	64	70	0.182	−0.159 to 0.522	1.045	0.296	3.918	0.270	23.432
Excluding null e-s	2	30	27	0.439	−0.091 to 0.968	1.623	0.105	2.374	0.123	57.872
et-PCO ₂ (mm Hg)										
Including null e-s	5	147	106	−0.283	−0.538 to −0.029	−2.180	0.029*	3.373	0.498	0.000
Excluding null e-s	3	113	63	−0.421	−0.731 to −0.110	−2.657	0.008*	0.382	0.537	0.000
<i>Venous parameters</i>										
Venous pCO ₂ (mm Hg)										
Including null e-s	2	32	37	−0.562	−1.039 to −0.085	−2.309	0.021*	0.156	0.693	0.000
Excluding null e-s										
Venous HCO ₃ (mmol/l)										
Including null e-s	2	32	37	−0.785	−1.270 to −0.299	−3.167	0.002*	0.061	0.805	0.000
Excluding null e-s										
Venous pH										
Including null e-s	2	32	37	−0.037	−0.512 to 0.438	−0.153	0.879	4.175	0.041*	76.051
Excluding null e-s										

* Fixed-effects models: $p < 0.05$; for Q statistics: $p < 0.1$. h = Hedges' g. e-s = Effect sizes.

Table 3. Meta-analysis of comparisons between PD and GAD groups

Baseline respiratory parameters	Studies, n	PD, n	GAD, n	Fixed-effects model				Heterogeneity		
				g	95% CI	Z	p	Q	p	I ²
<i>Mean</i>										
RR (breath/min)										
Including null e-s	5	191	131	0.259	0.029 to 0.489	2.203	0.028*	37.092	0.000*	89.216
Excluding null e-s	4	172	114	0.297	0.050 to .544	2.361	0.018*	36.371	0.000*	91.752
RR ^a (breath/min)										
Including null e-s	4	127	83	-0.218	-0.496 to .061	-1.530	0.126	1.934	0.586	0.000
Excluding null e-s	3	108	66	-0.269	-0.578 to 0.041	-1.700	0.089	1.385	0.500	0.000
MV (l/min)										
Including null e-s	3	55	45	0.250	-0.140 to 0.639	1.258	0.209	2.354	0.308	15.050
Excluding null e-s	2	36	28	0.397	-0.094 to 0.888	1.585	0.113	1.419	0.234	29.509
et-PCO ₂ (mm Hg)										
Including null e-s	5	147	96	-0.420	-0.683 to -0.158	-3.138	0.002*	9.256	0.055*	56.786
Excluding null e-s	4	128	79	-0.505	-0.793 to -0.217	-3.441	0.001*	7.312	0.063*	58.972

* Fixed-effects models: $p < 0.05$; for Q statistics: $p < 0.1$. h = Hedges' g. e-s = Effect sizes. ^a Excluding Munjack et al. [7].

exclusion procedure had already identified the outlying effect size of Munjack et al. [7] as the source of heterogeneity for this variable. No moderator analyses were significant (detailed results available upon request).

Publication Bias

Detailed results of Egger's regression tests are provided as supplementary data. Egger's regression tests were significant only for mean et-pCO₂ (PD vs. GAD) when the null-effect sizes were excluded from the analysis ($p = 0.016$). Instead, Egger's regression tests were not significant when effect sizes coded as null were inserted. As in [6], the strategy to include null-effect sizes to overcome the bias of unreported nonsignificant results was efficacious.

Discussion

Our meta-analytic results showed significant differences on baseline respiratory variables between subjects with PD and those with SP or GAD, supporting the idea of specific respiratory abnormalities in PD. Our findings should be considered preliminary because included studies allowed the meta-analysis of only a few respiratory variables and only fixed-effects meta-analytic models could be performed. Further independent studies are needed before more definitive conclusions. No evidence of publication bias was found, suggesting no concerns about possible unpublished data that we did not insert in our meta-analysis.

Comparisons between PD and SP

Subjects with PD showed significantly lower baseline mean et-pCO₂, indicating a condition of hyperventilation, and higher mean RR than subjects with SP, with small-to-moderate differences for both variables [22]. Although the point-estimate of the mean MV summary effect size was positive, suggesting higher global MV in PD, this result did not reach statistical significance, possibly because of the weak statistical power of the analyses. No significant differences were found for mean TV between groups. Higher mean RR in subjects with PD than in those with SP suggests that faster breathing might be a source of hyperventilation in PD. Unfortunately, no data were available to meta-analyze possible differences between PD and SP on indices of respiratory variability/irregularity or rate of sighs/apneas. In fact, these may be a source of hyperventilation in PD [6]. Thus, the available data do not allow fully disentangling the source of the baseline hyperventilation of subjects with PD compared to those with SP.

We also found lower venous partial pressure of CO₂, in line with the findings of lower et-pCO₂, and lower venous HCO₃⁻ concentrations in subjects with PD, whereas no difference in venous pH was found. The significantly reduced HCO₃⁻ concentration without a significant difference in pH suggests that the lower et-pCO₂ in subjects with PD might arise from chronic hyperventilation, also a condition existing before the experimental assessment procedures.

These findings are not in line with the few available studies employing ambulatory monitoring devices in real-life settings, which have failed to provide any evidence of hyperventilation in PD by comparing mean MV, RR and TV of subjects with PD and controls [19, 23–25]. The reasons for this discrepancy may arise from the limited statistical power achieved in the ambulatory monitoring studies, probably due to the small sample sizes, and from the lack of measuring key variables related to hyperventilation, such as end-tidal or transcutaneous pCO₂.

In summary, we found a condition of chronic hyperventilation in subjects with PD compared to those with SP.

Comparisons between PD and GAD

Subjects with PD showed significantly lower baseline mean et-pCO₂ than subjects with GAD, indicating a condition of hyperventilation. This difference was medium in magnitude [22]. Subjects with PD showed significantly higher baseline mean RR than subjects with GAD, but no significant difference was found after excluding the outlying effect size of the study by Munjack et al. [7] from the analysis. This study shows several methodological limitations, such as the lack of a diagnostic structured/semi-structured interview and the lack of screening of subjects' medical illnesses or respiratory diseases. Thus, the lack of difference on mean RR between PD and GAD seems to be a more reliable meta-analytic result. No significant differences were found for mean MV. Finally, no sufficient data were available to perform meta-analysis on baseline mean TV and other respiratory variables, such as indices of respiratory variability/irregularity or rate of sighs/apneas. For these reasons, the source of the baseline hyperventilation of subjects with PD compared to those with GAD cannot be found.

Limitations

The main shortcoming affecting our meta-analysis is the limited number of independent studies available for each comparison. Thus, there were only a few meta-anal-

yses of respiratory and hematic variables, whereas no analyses were performable for several other relevant variables related to respiratory function, including indices of respiratory variability/irregularity and rate of sighs/apneas. In addition, no data were available regarding other ADs than SP and GAD. Due to the small number of single-study effect sizes, only the fixed-effects model was able to be performed, providing less consistent results than the combination of fixed- and random-effects models. Furthermore, because of the weak statistical power, nonsignificant results may either reflect a real lack of difference among the compared groups or be a consequence of the small statistical power achieved by our analyses. Similar limitations may have affected moderator and publication bias analyses.

Other limitations arise from the general poor methodological quality of the studies performed in this field. Several studies did not apply some relevant exclusion criteria in the selection of their samples. When possible we included these variables as moderators, but, for instance, this strategy could not be used for the psychiatric comorbidity because none of the included studies had fully applied this exclusion criterion, and this constitutes a possible source of bias. Samples of subjects with PD and other ADs were often unbalanced for sociodemographic characteristics, thus introducing other potential sources of biases. For instance, gender has a well-known impact on respiration related to the influence of the menstrual cycle on many respiratory variables [26, 27]. Many studies reported data only regarding the significant effect sizes; in order to avoid possible biases arising from the exclusion of nonsignificant comparisons, we applied, when possible, a null-effect size inclusion – a strategy that had been efficacious in our previous meta-analysis [6].

Since the meta-analytic approach is strictly based on the quality of the included studies, a general methodological weakness of the entire field of research makes it difficult for meta-analyses to be applied and to provide reliable answers. In order to reach complete and reliable results, a greater number of independent studies comparing respiratory function between subjects with PD and subjects with other ADs, a greater completeness of the investigated variables, and better methodological designs are necessary.

Conclusions

Subjects with PD show a condition of baseline hyperventilation when compared with subjects with SP and GAD. Comparisons of hematic variables between PD and

SP suggest that the hyperventilation may be chronic and thus present also before and beyond the experimental respiratory assessment. Our findings support the idea that the respiratory abnormalities might be specific features of the PD pathophysiology not shared with other ADs. However, the source of these abnormalities remains unclear. They may arise from an intrinsic malfunction of the respiratory system, as proposed by [2–4], or be related to emotional/cognitive/behavioral factors [28, 29].

Studies in healthy subjects have found both a positive association between trait anxiety levels and mean RR during mental stress paradigms [30, 31] and increased ventilation with reduced et-pCO_2 during anticipatory anxiety when waiting for an electrical stimulation [32]. This suggests that anxiety experienced by subjects may modulate their respiration patterns [33]. Subjects with PD may experience more anxiety than subjects with other ADs during experimental laboratory procedures. This may partly explain the discrepancy in the results between ambulatory monitoring and laboratory studies on respiration. Previous studies have found that subjects with PD and those with GAD or SP exhibit equivalent trait anxiety [34–36], and most studies that have measured state-anxiety before respiratory assessment have found similar levels in subjects with PD and in those with GAD or SP [9, 36–38]. This indication, in association with the finding of chronic hyperventilation in PD, suggests that a general temporary condition of state-anxiety related to the experimental setting might not be able to fully account for the respiratory abnormalities of PD. On the contrary, subjects with PD exhibit peculiar emotional/cognitive/behavioral features, such as fear of somatic sensations, panic-specific beliefs and phobic/protective behaviors [39, 40] that perhaps are not completely captured by simply measuring general levels of trait/state anxiety [41]. Thus, these factors might influence respiration of subjects with PD in a peculiar way, leading to their specific respiratory abnormalities even when compared to subjects with other ADs and exhibiting similar levels of trait/state anxiety.

Further studies specifically investigating these issues are needed to clarify the source of the PD-specific respiratory abnormalities.

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