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Fear Responding to 35% CO₂ Challenge as a Vulnerability Marker for Later Social Anxiety Symptoms

Norman B. Schmidt, Ph.D.^{*}, Kiara R. Cromer, M.S., and Julia D. Buckner, M.S.

Florida State University

Abstract

The majority of biological challenge studies have focused on panic disorder though there is a small literature suggesting that patients with social anxiety disorder (SAD) show comparable responding. These cross-sectional studies suggest that CO₂ reactivity may be a marker of vulnerability to social anxiety. However, the nature of this association is unclear due to design limitations in this literature. The present report prospectively evaluated whether response to a 20% CO₂ challenge was predictive of later changes in social anxiety symptoms. A large nonclinical sample of young adults ($N = 404$) screened for Axis I disorders completed a 20% CO₂ challenge and were followed for approximately 18 months. Consistent with the vulnerability hypothesis, those showing greater reactivity to the CO₂ challenge showed increased social anxiety symptoms over time. This significant association was maintained after controlling for gender and trait anxiety. These data provide novel evidence suggesting that CO₂ sensitivity is predictive of the development of social anxiety symptoms.

Keywords

social anxiety; social phobia; fear; panic; anxiety; biological challenge

Biological challenge studies that evaluate fear responding to the ingestion or inhalation of a wide range of substances have long been utilized to evaluate the neurobiological underpinnings of panic and anxiety disorders (see Zvolensky & Eifert, 2000, for a review). Scores of challenge studies have determined that patients with anxiety psychopathology show increased reactivity in the context of challenge agents. For example, patients with panic disorder exhibit increased rates of challenge-induced panic attacks and fear responding to carbon dioxide-enriched air (CO₂) inhalation (Gorman et al, 1990). Despite considerable research focusing on panic and panic disorder (Feldner et al, 2004; McNally, 1990; Roth, 2005), only a relatively small literature has focused on other anxiety conditions such as social anxiety disorder (SAD). A review of SAD challenge studies suggests that these patients also experience increased fear responding to CO₂ challenge (Caldirola et al, 1997; Gorman et al, 1990; Papp et al, 1993). Some reports in fact suggest comparable fear responding between people with SAD and those with panic disorder (Caldirola et al, 1997; Caldirola et al, 1995).

While early reports consistently suggest exaggerated reactivity to challenge, relatively little follow-up research has focused on social anxiety. This is unfortunate since elaboration on such findings may yield important insights into the nature of social anxiety, as such studies have in

^{*}Corresponding Author. Norman B. Schmidt, Ph.D. Department of Psychology, Florida State University, Tallahassee, FL 32306-1270. Phone: 850-644-1707, Fax: 850-644-7739, Email: Schmidt@psy.fsu.edu.

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panic disorder. In a recent report, our group found that social anxiety symptoms were strongly associated with fear responding to a 35% CO₂ challenge and that this association remained after controlling for history of panic attacks and other potential confounding variables (Schmidt & Richey, 2007). This report, as well as others, suggests a significant and unique association between social anxiety and CO₂ reactivity.

The CO₂ challenge literature has led to propositions that CO₂-reactivity, that is, the tendency to respond to CO₂ with anxiety/fear, may be a risk marker for panic-related pathology. For example, Papp et al. (1993) suggest that CO₂ hypersensitivity may be a risk marker for the development of panic disorder. However, such studies have relied on cross-sectional designs and therefore leave unanswered the question of whether CO₂ reactivity truly serves as a risk factor for panic-related symptoms and diagnoses, or whether it is merely concomitant to the experience of panic symptoms. In a recent study, we addressed one of the key limitations of this literature by prospectively examining CO₂ hypersensitivity as a risk factor for panic and panic disorder (Schmidt et al, 2007b). This study found that CO₂-induced fear responding was a very strong predictor of future panic attacks but not panic disorder.

The main goal of the present study was to extend prior work by utilizing CO₂ hypersensitivity as a prospective risk variable (Schmidt et al, 2007b) in relation to social anxiety. Consistent with past research showing that patients with SAD have heightened fear responding to CO₂ (Caldirola et al, 1997), as well as work showing that social anxiety symptoms predict increased fear response to 35% CO₂ (Schmidt & Richey, 2007), we predicted that heightened response to CO₂ would predict increases in social anxiety symptoms over time. Furthermore, we attempted to rule out other competing hypotheses by evaluating whether challenge reactivity predicted social anxiety symptoms after controlling for other relevant predictors (e.g., general levels of trait anxiety). We also evaluated whether these effects were modulated by sex given substantial sex differences in SAD (Kessler et al, 1994; Wittchen et al, 1999).

Method

Overview of Study Design

These data are derived from a primary prevention study that included both an experimental and a prospective design. Participants with no current or recent psychiatric illness were randomly assigned to a brief risk reduction or control condition and followed for approximately 24 months (see Schmidt et al, 2007a). In the present report, we statistically controlled for experimental condition in all relevant analyses.

Participants

Sampling and Recruitment—The present study utilized a multi-stage recruitment process to target high-risk individuals from the Columbus, OH metropolitan area school system ($n = 46$), the Ohio State University ($n = 263$), and the Columbus, OH community ($n = 95$). The demographic makeup of the sample at entry was as follows: by design the sample was relatively young (age $M = 19.3$, $SD = 3.9$) with the majority being female (61%). The sample was also primarily Caucasian (74%) with 10% African-American, 9% Asian-American, 2% Hispanic, and 3% Other. Completion of college was the most frequently reported level of parental education with 30% of mothers and 29% of fathers finishing college.

Assessments

A multi-modal assessment battery was administered to all participants at baseline. This battery consisted of clinician-rated measures as well as self-rated measures. In addition, participants completed a 20% CO₂ challenge. During follow-up, the measures were repeated. Clinician raters were unaware of the participant's treatment condition.

Diagnostic Interview—To ensure the sample was nonclinical, structured diagnostic interviews (SCID-NP; First, 2001) were conducted at baseline. These interviews were completed by advanced graduate students in clinical psychology who had received extensive training in SCID administration and scoring. This training included reviewing SCID training tapes, observing taped SCID administration, observing live SCID administration, and conducting SCID interviews with a trained interviewer. Interviewers received feedback throughout this process until they demonstrated high reliability. These same training procedures have been used in other projects in our laboratory that have generated high inter-rater reliability for all Axis I diagnoses (Schmidt et al, 1997). A consensus method of diagnosis was used at weekly staff meetings where positive diagnostic findings were reviewed. Note that SCIDs were also completed at follow-up but there were insufficient SAD diagnoses to make for meaningful analyses. Thus, the present report focuses on changes in social anxiety symptoms.

Measures

Acute Panic Inventory (API): The API is a commonly used measure for assessing symptoms of arousal associated with panic attacks (Liebowitz et al, 1984). The API has been used extensively in panic provocation studies (Fyer et al, 1987; Gorman et al, 1994; Harrison et al, 1989; Schmidt et al, 2005). Participants rate the severity of each symptom (API-SXS) from 0 (absent) to 3 (severe). The API includes a SUDS rating of self-reported anxiety (0 - No Anxiety, 100 - Extreme Anxiety). In the present report, API-SXS and API-SUDS reactivity (pre-post API change) during the challenge served as the main predictors of interest.

Social Interaction Anxiety Scale (SIAS) and Social Phobia Scale (SPS): Due to the development of only a limited number of SAD diagnoses during the follow-up period, the primary outcomes of interest were changes in social anxiety symptoms. The SIAS assesses general social interaction fears and corresponds to the description of generalized SAD whereas the SPS assesses fears in which the person is the object of scrutiny (Mattick et al, 1998). The scales demonstrate high levels of internal consistency across clinical, community, and student samples (Heimberg et al, 1992 Hope, & Liebowitz, 1992; Mattick et al, 1998) and test-retest reliability in clinical and nonclinical samples (Heimberg et al, 1992; Mattick et al, 1998). Prior research indicates that cut scores on the SIAS and SPS correctly classified the majority of patients with SAD (Heimberg et al, 1992). These cut scores were used to identify participants with clinically significant social anxiety symptomatology in some of the analyses.

Trait Anxiety: Trait anxiety was assessed with the trait anxiety scale of the State Trait Personality Inventory (STPI; Spielberger, 1979). This scale is a well-validated self-report inventory that measures chronic (trait) anxiety.

20% CO₂ Challenge: A 20% CO₂-enriched (balance O₂) biological challenge provided an index of fear responding to a novel stimulus. The 20% CO₂ challenge methodology has been successfully used in a variety of other studies (Zvolensky & Eifert, 2000). To control for different expectancies regarding the consequences of breathing CO₂-enriched air, all participants were informed of several possible symptomatic consequences of breathing CO₂-enriched air including: breathlessness, dizziness, chest pain, and tachycardia. Participants were not informed regarding the onset, timing, dose, or offset of the inhalation of CO₂. Participants underwent a 20-s gas inhalation (20% CO₂, 80% O₂) administered through a continuous positive air pressure Downs C-Pap Mask with nose clip and head strap. Attached to one free port of a manually controlled 3-Way Stop Cock valve (Hans Rudolph, Inc.) was a 30-L meteorological balloon, which was inflated with the CO₂ mixture. Participants breathed the CO₂ gas directly from the balloon reservoir to minimize detection from pressurized CO₂ to non-pressurized room air. The C-Pap mask was connected to a free 22-mm port of the Stop

Cock Valve via 1.8-m of aerosol tubing and the remaining port was left unattached and fed room air. A remote device was used to control of the 3-Way Stop Cock valve for unobtrusive switching between CO₂-enriched air and room air.

Procedure

Following written, informed consent, participants completed the SCID and, if eligible, a battery of self-report measures. Eligible participants were then randomly assigned to one of two conditions (treatment or control). Both conditions involved information delivered via an audio-visual computer presentation lasting approximately 30 minutes followed by 10 minutes spent with an experimenter. Those assigned to the treatment condition received an intervention designed to reduce anxiety sensitivity whereas control participants received a control intervention that focused on health and nutrition but did not directly address anxiety sensitivity (see Schmidt et al, 2007a for details). Following the intervention, participants completed a CO₂ challenge. At this point, participants were led to a comfortable recliner in a dimly lit sound attenuated chamber and fitted with the CO₂ apparatus (e.g., mask). Participants completed an API following a 5-minute adaptation period. After approximately 3 minutes, participants received a 20-s inhalation of 20% CO₂-enriched air. Immediately following the inhalation, participants returned to breathing normal room air and completed another API. Community and high school participants received \$25 as compensation for the baseline assessment whereas college students received course credit.

Participants were followed for up to 24-months. During the follow-up evaluations, the self-report measures were re-administered to assess for social anxiety symptoms. All participants received \$25 for completion of a follow-up evaluation.

Results

Sample Size and Preliminary Analyses

At the outset, the sample included an initial assessment of 404 participants randomized to treatment condition (Treatment (47%): $n = 189$; Control (53%): $n = 215$). We were able to complete a follow-up evaluation with 295 participants at an average of 18 months post baseline. The n for various analyses varies to some degree depending on missing data. Those participants who did not complete a follow-up assessment did not differ from study-completers in terms of baseline demographics, clinical variables, cognitive vulnerability, CO₂ reactivity or condition (p 's $> .10$).

Manipulation check for the CO₂ Challenge

To evaluate whether the challenge produced reactivity, repeated measures ANCOVA was used to examine whether there was significant change in challenge anxiety outcome variables from baseline to postchallenge, after controlling for treatment condition. Consistent with expectation and prior work, the 20% CO₂ challenge produced significant increases in API-SUDS ($F(1,402) = 45.8, p < .001$, partial $\eta^2 = .10$), and API-SXS ($F(1,402) = 36.4, p < .001$, partial $\eta^2 = .08$).

Prospective evaluation of Social Anxiety and CO₂ Reactivity

Stepwise hierarchical regression analyses were used to ascertain whether baseline CO₂ reactivity predicted changes in social anxiety over time (see Table 1). In the first step, the baseline variable relevant to the predicted variable of interest (SIAS or SPS) was entered along with experimental condition, and STAI. In addition, the pre-CO₂ subjective index was entered in the first step (API-SUDS or API-SXS). In the second step, the corresponding API-SUDS or API-SXS score was entered thereby creating a residualized change variable for the CO₂ reactivity indices. We also included sex in the second step to examine the main effects of

gender. Finally, a sex $\times$ residual change on the CO₂ reactivity index was entered into step 3 of the equation to determine whether any effects were moderated by sex. This hierarchical model ensures that the observed effects of variables at each level are unique and cannot be attributed to variance with factors in the preceding levels (Cohen & Cohen, 1983). In total, we examined 4 separate equations.

As can be seen in Table 1, these analyses yielded a fairly consistent pattern of findings. In three of four cases, greater CO₂ reactivity at baseline predicted greater social anxiety during follow-up. The one exception (*Equation 2: SIAS & API-SXS*) was trending in the expected direction. There were no significant main effects for sex and it appears that sex did not moderate the effects of CO₂ reactivity. This is consistent with our main hypothesis that there is a unique association between anxious response to a CO₂ challenge and the development of social anxiety symptoms over time, regardless of gender or trait anxiety.

Computation of Level of Risk

To provide a level of risk associated with the CO₂ reactivity indices that is more readily interpretable and potentially more useful for clinical decision-making, risk ratios were calculated for subjective reactivity predicting social anxiety symptoms. In accordance with recommendations (Heimberg et al, 1992), respondents were classified as high or low social anxiety based on SIAS and SPS cut scores (e.g., SAIS: high social anxiety ≥ 34 , low social anxiety ≤ 33 ; SPS: high social anxiety ≥ 24 , low social anxiety ≤ 23). Next, the API SUDS variable was dichotomized to yield a grouping CO₂ reactivity variable. Similar to past studies, those showing SUDS increases >40 were assigned to the high reactivity group with the remainder assigned to the low reactivity group (Schmidt et al, in press). Hierarchical logistic regression analyses indicated that the odds ratio for CO₂ reactivity predicting high social anxiety symptoms was 2.0 ($Wald = 3.93, p < .05; 95\% CI = 1.01 - 4.02$) and 2.3 ($Wald = 4.07, p < .05; 95\% CI = 1.02 - 5.28$) for the SAIS and SPS respectively when controlling for experimental condition, trait anxiety and sex. Relative differences in social anxiety symptoms are graphically depicted for both SAIS and SPS using the CO₂ reactivity dichotomous variable (see Figure 1).

Discussion

The present study serves as the first known prospective investigation of the utility of fear responding to CO₂ challenge as a marker for the development of social anxiety. Our findings indicate that CO₂-reactivity is associated with the development of increased social anxiety symptoms, including clinically meaningful levels of social anxiety. This finding is consistent with cross-sectional studies that have found SAD to be linked to increase fear responding in the context of biological challenge studies (Caldirola et al, 1997; Caldirola et al, 1995; Gorman et al, 1990). We extended this work by determining that it appears to increased fear responding may serve as a risk factor for the development of social anxiety.

Garber and Hollon (1991) suggest three criteria for establishing whether a variable functions as a risk factor in psychopathology research. First, the vulnerability factor must be correlated with the outcome. Second, the vulnerability factor must demonstrate temporal precedence. Third, the relation between the vulnerability and outcome variables must be non-spurious (i.e., not due to a third variable). In regard to the first criterion, the present findings contribute to the growing body of research indicating increased fear response to biological challenge is related to social anxiety (Caldirola et al, 1997; Caldirola et al, 1995; Papp et al, 1993). Second, the present study provides the first known data suggesting that CO₂ reactivity temporally precedes increased rates of social anxiety. The present study also provides support for the third criterion, as the observed effects occurred even after controlling for relevant third variables

(e.g., trait anxiety, gender). Taken together, the present study serves as the most stringent test to date of the utility of CO₂ reactivity as a marker for the development of social anxiety.

The question arises as to why challenge-induced fear response is associated with increases in social anxiety. CO₂ hypersensitivity has been posited as a marker of vulnerability for a broader panic-phobic anxiety spectrum with panic attacks as a central feature (Perna et al, 1995). These explanations suggest that panic attacks may lead to the development of fear of fear in the case of panic disorder or anticipatory anxiety and avoidance of social situations in the case of social anxiety. Alternatively, cognitive behavioral models of social anxiety propose that maladaptive cognitions regarding possible scrutiny by others are believed to play an etiological and maintaining role in social anxiety (Hope et al, 2004). Exaggerated fear response results in external symptoms such as blushing, sweating, trembling, etc. Thus, for some people, experiencing these visible symptoms of anxiety may elicit concern that others will judge such reactions negatively. The CO₂ challenge may, for some, provide a gauge for such concerns. Additional experimental work is needed to illuminate the mechanisms linking CO₂ responding and social anxiety.

The finding that exaggerated fear response serves as a risk factor for increased social anxiety does not preclude the possibility that a reciprocal relation may exist between fear response and social anxiety. It may very well be that exaggerated fear response increases social anxiety and that this increased fear of negative evaluation results in hypervigilance for cues that signal possible scrutiny by others. This hypervigilance may result in physiological hyperarousal that increases anxious responding among these individuals thereby perpetuating and even increasing social anxiety. In fact, hypervigilance for threatening social cues among socially anxious individuals has been reported (Mogg & Bradley, 2002; Mogg et al, 2004) and is consistent with existing theoretical models of anxiety (Beck & Emery, 1985). The next step in this line of work is to examine the utility of such a forward-feeding cycle of fear response and social anxiety in the etiology and/or exacerbation of social anxiety.

In addition to implications regarding the etiology and maintenance of social anxiety, this work could provide valuable insight into the high rates of comorbidity among social anxiety and panic (Grant et al, 2005; Kessler et al, 2005). CO₂ reactivity has been posited to serve as a marker for a shared biological and/or psychosocial vulnerability factor for both panic and social anxiety (Caldirola et al, 1997). The present findings support this contention, as CO₂ reactivity was, in fact, associated with the development of increased social anxiety symptomatology. Our data suggest that future work is warranted to determine whether CO₂ reactivity is due to an underlying biological factor that increases risk of panic responding generally and/or anxiety conditions such as social anxiety and panic specifically.

Conclusions should be considered in light of limitations that suggest further work in this area. First, this study utilized a non-clinical sample in order to observe the prevention and onset of psychopathology. Replication with clinical samples is necessary to confirm the unique associations between CO₂ reactivity and the development of SAD. Second, the follow-up interval was relatively brief in the context of the development of psychopathology, which may have contributed to the low rates of psychopathology at follow-up. Future work should examine increases in social anxiety and incidence of SAD onset over longer intervals. Third, the sample consisted of participants in a primary prevention study. Although we statistically controlled for experimental condition, replication is warranted to assuage concerns regarding study design.

In sum, exaggerated fear responding may play a role in the development and/or exacerbation of social anxiety. Further work is necessary to determine whether CO₂ hypersensitivity serves as a biological marker for social anxiety development. Additional research is also warranted

to uncover biological and psychosocial mechanisms underlying increases in social anxiety among those who experience CO₂ reactivity. Combined with data from the present study, such work would have important implications regarding the treatment and prevention of social anxiety, as early treatment focused on assuaging fears others may negatively evaluate anxiety reactions could serve to prevent the development of social anxiety.

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Figure 1.
Social anxiety symptoms at follow-up relative to CO₂-responder status (high, low) at baseline.

Table 1
Cross-sectional association between Social Anxiety and CO₂ Reactivity

	R ² Total	F (step)	beta	t	p
Dependent Variable: SIAS at Follow-up					
Step 1	.35	.35			<.00
Condition			.11	2.06	.04
Baseline API SUDS			.01	0.27	.79
STAI			.02	0.29	.77
SIAS (Baseline)			.57	9.62	<.00
Step 2		21.3			<.00
Sex	.37		.05	0.84	.39
API-SUDS Reactivity					
Step 3 – Equation 1		18.3			<.00
Sex × API-SUDS	.37		-.09	-0.49	.63
Step 3 – Equation 2		18.4			<.00
Sex × API-SXS	.37		.13	0.73	.46
Dependent Variable: SPS at Follow-up					
Step 1	.34	28.3			<.00
Condition			.04	0.65	.52
Baseline API SUDS			-.03	-0.55	.58
STAI			.03	0.45	.65
SPS (Baseline)			.57	9.66	<.00
Step 2		20.2			<.00
Sex	.36		.08	1.39	.17
API-SUDS Reactivity			.15	2.16	.03
Step 3 – Equation 3		17.3			<.00
Sex × API-SUDS	.36		-.01	-0.03	.97
Step 3 – Equation 4		18.4			<.00
Sex × API-SXS	.37		.18	0.99	.32

Note: API Symptoms/SUDS = Acute Panic Inventory; STAI = Trait Anxiety scale from State Trait Anxiety Inventory; SIAS = Social Interaction Anxiety Scale; SPS = Social Phobia Scale.