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Which levels of cognitive impairments and negative symptoms are related to functional deficits in schizophrenia?



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ABSTRACT

Background: Negative symptoms and cognitive impairments predict difficulties

in aspects of everyday functioning in schizophrenia, with little research to date attempting to determine if there are threshold levels of impairment required to predict the severity of functional deficits.

Methods: People diagnosed with chronic schizophrenia (n = 821) were assessed with the MCCB and PANSS, and rated by high contact informants with SLOF. Negative symptoms of reduced emotional experience were specifically targeted for analysis because of their previously identified relationships with social outcomes. We identified patients with moderate negative symptoms (at least one PANSS item \geq 4) versus less severe symptoms (PANSS items \leq 3) and divided patients on the basis of a single latent-trait global cognition score (neuropsychologically normal vs neuropsychologically impaired; performance at or below 1.0 SD from the normative population mean, T = 40), then examined correlations between cognition, negative symptoms and everyday functioning in the groups with lower and higher negative symptoms and those with/without cognitive impairment.

Results: Even low levels of negative symptoms were correlated with ratings of social functioning. Cognitive performance in the neuropsychologically normal range, in contrast, was not correlated with any aspects of everyday functioning while more impaired performance predicted greater functional impairments.

Conclusions: Even minimal symptoms may be a target for clinical attention in the domains of negative symptoms, consistent with previous findings regarding social deficits in populations with modest negative symptoms (e.g., schizotypal personality disorder). Cognitive rehabilitation treatments might not improve social functioning if even low levels of negative symptoms (social amotivation) are present.

1. Introduction

Despite 50 years of intervention research, schizophrenia remains one of the leading causes of disability worldwide. Treatment resistance, as well as partial response, are prevalent, complicating the disability burden inherent in the disease. Despite relatively successful pharmacological treatment of positive symptoms, functional deficits remain commonplace, spanning critical areas of daily living such as independence in residence, gainful employment and social functioning (Velthorst et al., 2017). Setting aside positive symptoms and functional capacity, other established predictors of disability include cognitive deficits and negative symptoms, both of which are largely responsible for the refractory nature of disability in schizophrenia.

Negative symptoms and cognitive impairments are often present prior to the onset of frank psychosis defining schizophrenia and are frequently observed in prodromal (attenuated psychosis) cases (Seidman et al., 2010) and individuals with schizophrenia spectrum personality disorders (McClure et al., 2013). The presence of these symptoms at these phases is important because functional decline occurs early in the course of the illness and overall outcome has been observed to be directly correlated with functional ability prior to onset of psychosis (Carrion et al., 2011). Moreover, there is now considerable evidence that people with attenuated psychosis syndrome (APS), a relatively recently proposed diagnostic category, are affected by cognitive (Fusar-Poli et al., 2012) and negative symptoms as well (Lencz et al., 2004). This would suggest that the potential impact of cognitive and negative symptoms needs to be conceptualized as including time periods currently not previously considered pathological and with further delineation and investigation, should also open up the possibility of targeted preventative interventions early on.

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Schizotypal personality disorder (SPD) is defined by the presence of negative symptoms and social deficits in the absence of psychosis. Cognitive impairments are also seen in this population, with a profile of performance similar to that seen in schizophrenia but with attenuated severity. Importantly, everyday functional outcomes are affected in people with schizotypal personality disorder and the correlation between indices of cognition and functional capacity are similar to those seen in schizophrenia (McClure et al., 2013). Further, schizotypal personality disorder also has a number of features in common with attenuated psychosis syndrome and people with schizotypal personality disorder may constitute a portion of the group of APS cases who never develop a psychotic condition but who manifest lifelong social deficits.

The relationship between cognitive and negative symptoms is not a simple one. Cognitive and negative symptoms are related but separable domains with different functional implications, in that negative symptoms may partially mediate the longitudinal relationship between cognition and outcome (Ventura et al., 2009), in addition to a having a direct influence on certain aspects of functional outcomes. Moreover, cognition and negative symptoms appear to affect various outcome domains (work, residence, and social achievements) differentially (Bowie et al., 2008). Further, these elements of everyday functioning are minimally intercorrelated in people with chronic schizophrenia, suggesting that global indices of disability may lack the requisite specificity, and more domain-specific outcome measures would better serve to define adaptive functioning (Leifker et al., 2009).

To that end, we recently reported that negative symptoms predicted the severity of social deficits, but did not contribute to predicting realworld performance of everyday activities and vocational outcomes (Strassnig et al., 2015). Similarly, cognition and functional capacity were predictors of the severity of deficits in performing everyday activities and vocational outcomes, but did not predict social functioning. In a further analysis of these data, we reported that the negative symptoms from the PANSS that measure reduced emotional experience, <u>social motivation, and engagement</u> (anhedonia/avolition) were related to social outcomes, with no other negative symptoms, largely from the domain of emotional expressiveness, correlating with any aspect of real world outcomes (Harvey et al., 2017).

Pharmacological advances aimed at treating both negative (Bugarski-Kirola et al., 2017) and cognitive symptoms (Keefe et al., 2017) have not been successful, whereas some success has been achieved in treating cognitive impairment with CRT, transferring into real world-gains if paired with specific skills training programs (Bowie et al., 2012). The benefits of cognitive remediation may extend beyond cognition and result in small to moderate improvements in negative symptoms (Cella et al, 2017a, 2017b) and social functioning (Ventura et al., 2017). The literature has not examined, however, whether there is a predictive relationship between symptom severity and functional deficits at different levels of severity of impairment. It is entirely possible that severe cognitive and negative symptoms are more difficult to treat than milder symptoms. Evidence from pharmacological studies of schizotypal personality disorder suggest that interventions with minimal efficacy in chronic schizophrenia (Friedman et al., 2008; Girgis et al., 2016) can have notable impacts on cognition in that less impaired population (McClure et al., 2007; Rose ll et al., 2015). As we note above, populations with reduced levels of cognitive performance and less substantial negative symptoms than those seen in typical chronic patients also manifest deficits in social and vocational outcomes. We hypothesize that such lower, but measureable, levels of cognitive impairment and negative symptoms may still influence everyday outcomes but their relevance remains unclear.

In this paper we examine correlations between cognition, negative symptoms affecting reduced emotional experience, and everyday functioning in the groups with lower and higher levels of these negative symptoms and those with/without cognitive impairment. Our aim is to establish whether there are threshold levels of reduced emotional experience negative symptoms and cognitive impairments that would be associated with impairments in functional outcome. In specific, we examine the correlations between cognitive performance and reduced emotional experience negative symptoms and three different domains of functional outcome (social, vocational, and everyday activities) in people with negative symptoms with greater and lesser levels of severity and in patients whose cognitive performance was putatively "neuropsychologically normal" vs. impaired. As the sample size is considerable in this sample, the relatively lower expected prevalence of normal performance does not lead to a limitation of statistical power, in line with previous studies (Heinrichs et al., 2015; Granger et al., 2018). Unimpaired cognitive performance can be defined on the basis of historical definitions of neuropsychologically normal performance. However, the Definition of more vs. less severe negative symptoms lacks similar normative standards. In our previous studies we found that correlations between a single negative symptom reflecting reduced emotional experience (passive-apathetic social withdrawal; Robertson et al., 2014) shared as much as 25% of the variance with clinician rated real world social outcomes. Thus, a single negative symptom at moderate or higher levels of severity appears clinically important and this guided our definition of moderately severe vs. less severe reduced emotional experience negative symptoms.

Our hypotheses was that even within patients whose reduced emotional experience and global negative symptoms were less severe and in patients with neuropsychologically normal cognitive performance we would find correlations between reduced emotional experience negative symptoms and cognitive deficits and everyday functioning across the three functional domains we have previously studied.

2. Methods

The sample of patients and their assessments was previously reported on by Strassnig et al. (2015). We will review the details of the previous study briefly.

2.1. Participants

The data are part of four study cohorts collected in five different geographical areas within the United States, aimed at identifying the course and correlates of change in functional status as well as the optimal method for rating everyday functioning among schizophrenia outpatients.

The study participants were stable patients with schizophrenia or schizoaffective disorder receiving treatment at one of several different outpatient service delivery systems in Atlanta, Dallas, Miami, San Diego and New York City. All research participants provided signed informed consent per standards approved by the responsible local Institutional Review Boards. These data were collected between March 2003 and May 2014.

All enrollees completed a structured diagnostic interview, administered by a trained interviewer. The Structured Clinical Interview for the DSM (SCID; First et al., 2002) was used at the Atlanta sites, the Mini International Neuropsychiatric Interview, 6th Edition (Sheehan et al., 1998) in Dallas, San Diego, and Miami, and the Comprehensive Assessment of Symptoms and History (CASH; Andreasen et al., 1992) in New York; all diagnoses were verified in local consensus procedures. Patients were excluded for a history of traumatic brain injury, brain disease such as seizure disorder or neurodegenerative condition, a reading score below the 6th grade in all samples, or the presence of another DSM-IV diagnosis that would exclude the diagnosis of schizophrenia. These procedures were described in previous publications.

2.2. Assessment strategy

Real world functioning was rated with the Specific Levels of Functioning (SLOF; Harvey et al., 2011) across all study cohorts. Across the studies, ratings were generated by a high-contact clinician, either a

Table 1

Functional outcomes, cognitive performance, and negative symptoms in higher and lower performing groups.

	Neuropsychologically					Lower Experience Negative		Moderate Experience Negative		
			Impair	red	_	Symptoms		Symptoms		
			N = 367		_	N = 394		N = 160		
	М	SD	М	SD	_	М	SD	М	SD	
SLOF Variables										
Interpersonal Functioning	26.6	6.1	25.4	6.7	t = 2.12, p = .035	27.5	6.2	21.7	5.7	t = 10.2, p < .001
Everyday Activities	52.0	5.5	47.3	10.5	t = 5.2, p < .001	48.4	8.7	50.3	10.9	t = -1.88, p = .06
Vocational Outcomes	24.6	4.7	21.9	5.7	t = 5.4, p < .001	23.0	5.6	22.5	5.3	t = 1.03, p = .32
Composite Cognitive Performance	44.9	4.1	32.8	5.2	t = 27.9, p < .001	36.7	7.6	37.0	7.8	t =46, p = .65
Reduced Emotional Experience	7.1	3.6	7.0	3.5	t = .24, p = .81	5.1	2.0	11.2	2.5	t = 32.6, p < .001

1. T-scores with a mean of 50 and SD of 10. NP normal is defined as t-score greater than 40.

2. Based on three PANSS items with possible scores ranging from 2 to 21.

case manager, a residential facility manager, or a psychotherapist who reported knowing the patient "very well". The original SLOF was abbreviated to assess 5 functional domains from which we selected the following domains to be examined in all studies: *Interpersonal Functioning* (e.g., initiating, accepting and maintaining social contacts; effectively communicating), independent participation in *Everyday Activities* (shopping, using telephone, paying bills, use of leisure time, use of public transportation), and *Vocational Functioning* (e.g., employable skills, level of supervision required to complete tasks, ability to stay on task, completes tasks, punctuality). The dependent variables for the statistical analyses were the scores on these three different subscales. Cases with missing functional data were excluded from further analysis.

2.3. Negative symptoms assessment

Severity of negative symptoms was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, 1991), which was administered in its entirety by trained raters who did not perform the functional outcomes ratings. These ratings were performed for the entire PANSS and the subsequent subdivisions of the data occurred after the ratings were collected.

2.4. Cognition

As described in the previous paper (Strassnig et al., 2015), slightly different cognitive batteries were used across the studies, reflecting the development of cognitive assessment in schizophrenia culminating in the MATRICS consensus cognitive battery (MCCB; Green et al., 2004). As these procedures were described in detail previously, we provide some minimal details and refer the reader to the previous publication. In that previous study, in order to examine the conceptual equivalence of the different cognitive batteries, we developed a cognitive performance latent trait, using the common tests across the samples. These included overlapping tests of processing speed, verbal fluency, working memory, and verbal learning and memory. We then demonstrated that this latent trait had the same correlations with functional capacity and real world functioning in each of the samples. We then took the tests included in the latent trait and converted them to t-scores using previously published norms, including the norms from the MCCB in three of the four samples. See Bowie et al. (2006) for a description of the norming of the earlier data. These t-scores were then averaged within the groups to create a composite score and used to subdivide the groups and to perform the correlational analyses.

2.5. Definition of unimpaired performance

Several previous definitions of neuropsychologically normal performance have been applied. In the absence of thorough evidence regarding premorbid functioning, several studies (Palmer et al., 1997; Reichenberg, 2010; Leung et al., 2008; Heinrichs et al., 2015) have used criteria of performance within one standard deviation below the normative mean or better being "unimpaired" or "neuropsychologically normal". We used this definition in this study as well, defining impaired performance as having an average t score of 40 or less based on the norms applied to that study (with a score of 50 being in the mean level of performance and an SD of 10).

2.6. Negative symptom models

Based on the previous report of Khan et al. (2013) a 2-factor model of expression and experience was developed and replicated in multiple samples. (Stiekema et al., 2016; Jang et al., 2016). The items in each of the factors were:

PANSS Reduced Expression: PANSS Blunted Affect (N1), Poor Rapport (N3), Lack of Spontaneity (N6), and Motor Retardation (G7).

PANSS Reduced Emotional Experience: Emotional Withdrawal (N2), Passive Social Withdrawal (N4) and active social avoidance (G16).

As we knew that the scores for PANSS reduced expression subscale were uncorrelated with the SLOF subscales, we examined the PANSS reduced emotional experience items and PANSS Marder Factor Total scores only. We created a total score for the reduced emotional experience subscale. Then we divided the patients into two groups, based on the rationale described above: those with at least one of the three PANSS items scored at 4 or more (moderate reduced emotional experience symptoms) and those without a single item rated as 4 or more. We similarly designated patients as having moderate overall negative symptoms using a similar strategy. Two of the six items being scored at moderate or high led to the designation of overall moderate negative symptoms.

3. Results

Supplemental Table 1 presents demographic data across samples, in line with our prior publication (Strassnig et al., 2015). Table 1 presents the scores on the functional outcomes measures and the cognitive and

negative symptoms predictors. There were 821 patients in the original sample and 554 patients with no missing data. Of the 554 patients, 367 (66%) were cognitively impaired according to our criteria, as outlined above. There were 160 (29%) of the cases with moderate reduced experience symptoms according to our criteria. There were also 128 cases (23%) with overall moderate negative symptoms. As can be seen in the table, participants meeting our predefined criterion for cognitive impairment on neuropsychological testing were significantly more impaired in all three functional outcomes domains, but there were no differences in reduced emotional experience symptom severity across the three groups defined by their cognitive test performance. Patients with moderate reduced emotional experience symptoms were more functionally impaired in interpersonal functioning than patients with less severe symptoms, but there were no differences in everyday activities, vocational functioning, or neuropsychological performance. When the same analyses were repeated with overall moderate negative symptoms, the results were essentially identical: the patients with overall moderate overall negative symptoms were significantly more impaired in interpersonal functioning, t (553) = 7.92, p < .001, than those without, and no other differences were significant, all t < 1.44, all p > .11. As expected, patients who were selected to have lower and higher cognitive test performance differed significantly from each other.

3.1. Negative symptoms and cognition predicting functional outcomes

Table 2 presents the Pearson Product Moment Correlations between cognitive performance, reduced emotional experience negative symptoms, and the different elements of functional outcomes. These correlations between cognition and negative symptoms are presented for the whole sample and separated on the basis of level of severity.

3.1.1. Reduced emotional experience and functional outcomes

The severity of reduced emotional experience negative symptoms was correlated with SLOF interpersonal functioning in all patients, lower severity patients, and patients with moderate or more severe negative symptoms (Table 2). Shared variance was 21% for the total sample and very similar at 8% for the lower severity and 5% for moderate severity subgroups. Reduced emotional experience negative symptoms did not predict independence in residence in the total sample or either of the two severity-based subgroups. They shared 1% variance with work outcomes in the overall sample and 4% variance in the moderate negative symptoms sample, but did not correlate with work outcomes in lower severity negative symptom subgroup.

Upon further analysis, when similar correlations were computed for the overall negative symptoms, the correlation with interpersonal functioning for the full sample was statistically significant, r = .41, p < .001, $R^2 = .16$. The correlation with work functioning was also significant, r = .14, p < .05, $R^2 = .02$, but the correlation with activities was not, r = .03, p = .97. For the sample with moderate overall negative symptoms, the correlation between interpersonal functioning and negative symptoms was significant, r = .36, p < .001, $R^2 = .13$, as was the correlation with work functioning r = .23, p < .01, $R^2 = .05$. Again, everyday activities was not correlated with negative symptoms. For the lower severity group, interpersonal functioning was correlated with negative symptom severity, r = -.35, p < .001, $R^2 = .12$. Identically to the group overall, the correlation with work functioning was also significant, r = .14, p < .05, $R^2 = .02$, but the correlation with activities was not, r = .06, p = .21.

3.1.2. Cognition and outcome variables

Cognitive test performance was correlated with interpersonal relationships, everyday activities, and work skills in the overall sample. The shared variance for these correlations was 1%, 12%, and 26% respectively across the three functional domains. In contrast, in patients with neuropsychologically normal t scores of > 40, there was no significant correlations with interpersonal relationships, everyday activities, or work outcomes. In patients with neuropsychologically impaired t scores \leq 40, both everyday activities and work were correlated with cognitive test performance with shared variance at 5% and 3% respectively.

4. Discussion

Persistent negative symptoms and cognitive deficits represent major independent factors determining everyday functioning in schizophrenia, and are present to varying degrees in most patients. While it is known that the severity of negative symptoms and cognitive deficits correlates with adaptive functioning, little research has been devoted to establishing thresholds at which the level of severity negative symptoms and cognitive deficits become functionally relevant. The relevance of subthreshold symptoms extends beyond schizophrenia, because negative symptoms and cognitive deficits are also commonplace in prodromal (i.e., attenuated psychosis) cases and individuals with schizophrenia spectrum personality disorders including SPD. In these two populations, performance profiles are similar to that seen in schizophrenia but with attenuated severity. Moreover, schizotypal personality disorder also has a number of features in common with attenuated psychosis syndrome, a recently proposed diagnostic category aimed at formally conceptualizing prodromal states.

Analyzing a large sample of well characterized patients, we found that in a group of patients where not a single reduced emotional experience negative symptom reached criteria for moderate severity there was still a significant negative relationship with everyday social functioning. Similarly, when 2 or fewer out of 7 overall negative symptoms were moderate in severity, overall negative symptoms still predicted social and work functioning. Cognitive performance in the neuropsychologically normal range, in contrast, was not correlated with any aspects of everyday functioning. Specifically, amongst the outcome domains measured in our sample - the ability to live and work independently, and effectively maintain interpersonal relationships – only comparatively higher levels of neuropsychological impairment

Table 2

Correlations Between Functional Outcomes	, Cognitive Performance	e, and Negative Symptoms i	n Higher and Lower Performing	Groups as well as the Total Sample.
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SLOF Variables	Total Sample	Neuropsychologie	cally	Total Sample	Lower Experience Symptoms	Moderate Experience Symptoms	
		Normal	Impaired				
	(n = 554)	(n = 187)	(n = 367)	(n = 554)	(n = 394)	(n = 160)	
Interpersonal Functioning	10*	12	03	-46***	28**	23**	
Everyday Activities	35**	07	25**	02	02	17	
Vocational Outcomes	51***	13	18*	-10*	04	22**	

*p < 0.05.

**p < 0.01.

***p < .001.

were associated with lower scores on the outcome domains, vocational and interpersonal functioning.

There were several other findings of interest. Higher and lower levels of reduced emotional experience negative symptoms were not associated with differences in cognitive deficits. The same was true for variation in cognitive deficits and their relationships with reduced emotional experience negative symptoms. The greater variation in severity scores for negative symptoms in the full sample led to larger correlations for social outcomes than for the two subgroups selected for an intrinsically truncated range of performance. The same was true for cognitive performance, wherein the full sample the correlations with everyday functioning were larger. However, the smaller sample size for the neuropsychologically normal sample cannot be a differential reason for reduced correlations: patients with moderately severe reduced emotional experience negative symptoms were also less than half the sample and the power in this sample size is considerable.

Despite a surge in interest in treating negative symptoms, options remain limited (Keshavan et al., 2017), with some promising reports from CRT, with CRT often delivered in a wider psychosocial training framework (Granholm and Harvey, 2018). Psychotherapeutic interventions to target negative symptoms have been ineffective or minimally effective (Grant et al., 2012; Velligan et al., 2015). Effective pharmacotherapies for cognitive and negative symptoms do not currently exist (Talpos, 2017). Based on recently completed trials, and an increasingly cost-prohibitive development process of novel therapies for schizophrenia, a major advancement in treating cognitive and negative symptoms in schizophrenia remains elusive. However, as with specific domains of cognitive deficits having differential impact on functional outcomes (Green et al., 2000), the conceptualization and measurement of negative symptoms requires more work to determine their collective and individual relation with outcome domains (Marder and Galderisi, 2017). For example, most trials enroll participants with relatively high negative symptom burden which may constitute the most refractory and least engaged patients. Applying such overly narrow negative symptom criteria may curtail the potential patient pool for trials (Rabinowitz et al., 2013). In line with our results, even low levels of 'core' negative symptoms such as reduced social motivation have functional relevance, but potential benefits of treatment in this group may be overlooked in trials recruiting patients on the basis of generally higher levels of symptom severity. Moreover, it is also possible that changes in negative symptoms are also more prominent if positive symptoms are mild over the lifetime course. Taken together, this would suggest to focus on lower severity patients, perhaps earlier in the course of their illness (Albert et al., 2017).

As we noted above, it has already been shown that pharmacological interventions impact cognitive performance in patients with nonpsychotic conditions in the schizophrenia spectrum, with several drugs showing a greater impact in SPD than in schizophrenia. These SPD patients had levels of cognitive performance that were better than that seen in schizophrenia patients. However, many of these patients had performance on neuropsychological tests would have still met our criteria for neuropsychological impairment. These results suggest that cognitive enhancement strategies should be targeted at individuals with more substantial cognitive impairments, regardless of their diagnosis (Granger et al., 2018). Performance that would be generally considered to be in the neuropsychologically normal range was not significantly correlated with everyday functioning.

There are some limitations of these data and these analyses. All patients had to be able to participate in an extensive in person assessment. This may have eliminated some patients with lower levels of functioning. All patients were selected for having a high contact informant who was willing to provide ratings. The proportion of cases with "neuropsychlogically normal" performance is higher than in some previous studies, but is consistent with that seen in clinical trials of patients with schizophrenia. These patients are perhaps easier to recruit into or retain in such trials – see Granger et al. (2018). The most

plausible reason is that more impaired cases are more likely to be missing data on functioning and were not included in the subsample. This would seem likely to bias the results in a direction opposite of what we found. Our cognitive assessment was limited by the need to focus on overlapping cognitive tests administered over a decade-long period wherein substantial refinement of the strategies used to assess cognition occurred.

Treatment implications include the adverse impact of even low level negative symptoms. Low level negative symptoms predicted social functioning while low level cognitive deficits did not predict any domain of functional outcomes. Thus, cognitive rehabilitation treatments still might not improve social functioning if even low levels of negative symptoms are present and leading to social amotivation. They might also not effectively improve the other outcome domains, work and residential independence, if cognitive deficits are modest or minor at the start of treatment. The greatest relative improvements in work and activities might be expected from cognitive remediation of the more cognitively impaired patients. Meta-analyses and the results of other analyses of this large sample of data have suggested that cognitive deficits are less strongly related to social deficits, when compared to the influence of social cognition (Fett et al., 2011). We did not measure social cognition in all of the samples analyzed, although in those where we did we found that social cognition was more strongly predictive of social outcomes than other predictors (Kalin et al., 2015).

The fact that low levels of negative symptoms were detrimental also highlights the need for developing treatments in APS and schizotypal PD and for those conceptualized under the APS syndrome, including those who do not develop active psychosis. There is currently no pharmacological treatment indication for this group of patients, and we suggest that these measurable, albeit low levels of negative symptoms should be focus of intervention. It is possible that the less prominent symptoms may allow for treatments that have failed in schizophrenia can be effective in this group, especially if utilized early in the course.

5. Limitations

Higher doses of antipsychotics could be a proxy for greater illness severity or greater positive symptoms and the levels could have led to lower functioning and greater negative symptom impairment.

Conflicts of interest

Dr. Harvey has received consulting fees or travel reimbursements from Allergan, Boehringer Ingelheim, Lundbeck Pharma, Minerva Pharma, Otsuka Digital Health, Sanofi Pharma, Sunovion Pharma, and Takeda Pharma during the past year. He has a research grant from Takeda and from the Stanley Medical Research Foundation.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https:// doi.org/10.1016/j.jpsychires.2018.06.018. References

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