Commentary

Biological Psychiatry: GOS

Negative Schizotypy: Now That We Know What It Is, Should We Do Something About It?

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In a new study in *Biological Psychiatry: Global Open Science*, Wang *et al.* (1) provide a detailed review of negative schizotypy (NS), clearly placing it in both its historical and contemporary context. Showing the areas of separation from positive and disorganized schizotypy and delineating NS from conditions with higher risk for conversion to psychosis, they review symptoms, cognition, and neurobiology as measured with various neuroimaging strategies and potential neurochemical alterations indexed with magnetic resonance spectroscopy. They note that NS is associated with increased vulnerability to psychosis, but that these NS features can also be shared across psychiatric conditions and that risk of conversion is now estimated to be relatively low, particularly in cases who have already experienced an apparent prodromal state and have never shown any psychotic symptoms.

There are 2 questions worth discussing. 1) What are the longitudinal characteristics of NS, and 2) are there possible treatments to reduce the disability?

One of the ways that persistent NS is detected is in individuals who were originally identified as prodromal (at-risk mental state, ultra-high risk, clinical high risk) who never converted to psychosis and never remitted from their schizotypal symptoms. Many different prodromal studies have identified high prevalence of these cases together with their continued impairments and lack of conversion to psychosis spanning 10 years or more. In an important study, Lam *et al.* (2) examined the longitudinal course of clinical high-risk individuals and found low rates of conversion and higher proportions of remission and nonremitting nonconverters. Cognitive and functional impairments at baseline were worst in the converters, changed the least in the nonremitters, and fully resolved in the remitters. The nonconverting nonremitters had residual cognitive impairments and disability, which was stable until the end of the follow-up period. Thus, these individuals manifested a stable impaired state, which seems to notably resemble the NS described by Wang *et al.* and is associated with considerable morbidity as described below.

Other studies of individuals ascertained as adults noted that cognitive impairments and everyday disability are commonly found, with performance-based measures of functional capacity also being affected (3). Employment outcomes are commonly reduced, compared with those of individuals with other personality disorders (PDs), such as avoidant PD (4). As noted by Wang *et al.*, pervasive impairments in social cognition and neurocognition have been detected, with profiles of impairments that seem notably similar to those seen in schizophrenia or even bipolar depression. These impairments are functionally relevant in general and possibly suggest that treatments developed for schizophrenia across its course could be beneficial.

There are several pharmacological cognitive treatment studies in samples of participants with schizotypal PD, and the predominant symptom presentation of those samples was congruent with the NS conception. Several different medications have shown efficacy, including the alpha-2 norepinephrine agonist guanfacine (5), the D_1D_2 agonist pergolide (6), and the D_1 agonist dihydrexidine (7). An interesting insight into the relative feasibility of treatment of NS also comes from these studies in that participants with schizophrenia who had been treated with both guanfacine and dihydrexidine failed to manifest a beneficial cognitive response. It is certainly possible that the co-administration of antipsychotic medications to participants with schizophrenia had an adverse impact on treatment benefits.

Two medications in later-stage development may have potential in NS. KarXT, an M_1M_4 muscarinic agonist, is close to U.S. Food and Drug Administration approval as an antipsychotic medication, but in 2 separate reports spanning 3 different clinical trials, the medication separated from placebo for cognition in acute treatment studies (8). Iclepertin, a glycine transport (GLYT-1) antagonist targeting the NMDA receptor system demonstrated efficacy in phase 2. This treatment is being developed as a co-administered add-on therapy for stable participants with schizophrenia receiving antipsychotic medications, so its use in unmedicated participants with NS could be quite interesting.

In one study reported to date, the combination of guanfacine and cognitive remediation training was found to improve cognitive performance and indices of functional capacity more than cognitive remediation training alone [McClure *et al.* (9)]. This strategy, pharmacologically augmented cognitive training, has been tried with several different augmentation agents in schizophrenia. In contrast to pharmacological treatments alone, pharmacologically augmented cognitive training interventions have shown efficacy in schizophrenia, suggesting that this is a strategy that may overcome disadvantages associated with antipsychotic treatments.

In-person training for social cognitive deficits and related social dysfunctions has been commonly used in schizophrenia. Such interventions are generally delivered by highly trained therapists and are not widely available other than at specialty centers, highlighting the potential importance of computerized interventions targeting this domain.

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Of course, negative symptoms are the central feature of NS, and pharmacological interventions in development for negative symptoms seem applicable to this condition as well. Pharmacological efforts for negative symptoms have not led to an approved treatment, and there is less positive information available even at the preliminary or phase 2 level about their effectiveness as cognitive enhancers. One medication that seems well aligned with the treatment of NS is roluperidone, a serotonin 2A antagonist that also interacts with the sigma receptor site. In 2 separate studies, roluperidone monotherapy administered to clinically stable participants with schizophrenia separated on both clinical ratings of negative symptoms and functional disability (10). This medication is undergoing regulatory assessment, with one of the official reasons that the treatment has not been approved yet being concerns about potential drug-drug interactions with antipsychotic medications, an issue that would not be relevant in the treatment of NS.

Interestingly, a pharmacologically similar agent, pimavanserin, was recently reported by its manufacturer to fail to separate from placebo in a targeted study of negative symptoms in patients with schizophrenia confirmed to be adherent to antipsychotic medications. The parallels with the effects of guanfacine and dihydrexidine are quite interesting because both of those medications enhanced cognition in participants with a diagnosis of schizoptypal PD with no concurrent antipsychotic therapies administered.

One of the issues that has been well researched in schizophrenia that clearly requires attention in NS is anosognosia and its impact on everyday functioning. Unawareness of illness is fundamental in schizophrenia, and it has been found to correlate with several different symptoms, including symptoms of both psychosis and avolition. In addition to not being able to recognize their symptoms as abnormal, those with schizophrenia are challenged in evaluating the quality of cognitive performance and everyday functioning. This is commonly referred to as a reduced introspective accuracy, which can then lead to response biases when assessment errors are made. The typical response bias is overestimation of functioning, and individuals with significant negative symptoms, such as social withdrawal and reduced motivation, have been noted to report that their functioning is considerably better than objective data suggest. These challenges can sustain negative symptoms by undercutting patients' motivation to change their life circumstances and engage in therapeutic activities such as vocational or educational assistance. Reduced awareness and challenges in introspective accuracy are correlated, at least moderately, with cognitive deficits. As a result, it would be likely that such processes are operative in NS and that their assessment could clarify more of the contributors to reduced functioning.

In conclusion, Wang *et al.* clearly describe the cognitive, social cognitive, and negative symptom underpinnings of impaired functioning in NS, which lead to substantial and persistent disability in schizophrenia and other conditions. This disability has been reported to be present in schizotypal PD, and it seems most likely that the NS group would be most affected. In this commentary, I describe the state of the art for treatment of neurocognitive and social cognitive deficits, impairments in functional capacity, and negative symptoms. The data are suggestive of likely greater success in treatment of these domains in NS than in schizophrenia because reduced risk of psychosis precludes the need for antipsychotic treatments. Drugs that fail in schizophrenia could very well work in NS, suggesting that a more intensive effort may be important.

One other issue is the timing of the intervention. The authors present evidence that detectable NS shows up earlier in the developmental course, prior to symptoms that could be considered prodromal, and then a slight worsening of symptoms is detected in cases whose condition shifts toward attenuated psychotic symptoms or psychosis. If NS symptoms are a precursor to multiple adverse outcomes and underlie a persistent functional challenge to those whose NS is temporally stable, then treatment of the syndrome pharmacologically, with cognitive training, and with other psychosocial interventions as early as possible could have a preventive effect on the later course of development of other schizophrenia-related conditions. This possibility has been suggested previously. With medications and training interventions now available with demonstrated efficacy in the domains of impairment in NS, directing research toward treatment development is as important as conducting additional descriptive research on the characteristics of NS.

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Article Information

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