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Author for correspondence:
Amy E. Pinkham, E-mail: amy.pinkham@utdallas.edu

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The benefit of directly comparing autism and schizophrenia, revisited

Amy E. Pinkham[1,2] and Noah J. Sasson[1]

[1]School of Behavioral and Brain Sciences, The University of Texas At Dallas, Richardson, TX, USA and [2]Department of Psychiatry, University of Texas Southwestern Medical School, Dallas, TX, USA

In his comment on our article, 'Comprehensive comparison of social cognitive performance in autism spectrum disorder and schizophrenia' (Pinkham et al., 2019), Crespi argues that reporting data indicating behavioral similarities between disorders may be of limited utility because they provide little actionable information about diagnosis, causes, or treatments. Although we agree with his primary point that behavioral overlap can emerge from distinct mechanistic origins, we disagree that similarities in social cognitive performance in autism spectrum disorder (ASD) and schizophrenia (SCZ) are without nosological or clinical value, particularly when revealed through well-controlled, large samples using psychometrically validated measures. We believe that behavioral convergence between disorders is important to acknowledge – and contrary to his claim that they obscure mechanistic and clinical distinctions – we think that they can provide a strong and necessary starting point for more targeted studies aimed at uncovering and understanding mechanisms and informing effective treatments. In the response below, we highlight areas of agreement with Crespi but also offer several counterpoints to each of the considerations he uses to support his argument.

First, Crespi comments that similar behavioral outcomes can result from similar, partially overlapping, or even opposing (Crespi & Badcock, 2008), biological causes and that the data we report may inadvertently imply mechanistic similarities. While we fully agree that basic performance-based social cognitive comparisons between ASD and SCZ cannot address mechanism, we disagree that behavioral similarities necessarily imply mechanistic ones. Indeed, we explicitly caution against such an interpretation in the paper's discussion and have previously written extensively, both in empirical (Morrison et al., 2017; Sasson et al., 2007; Sasson, Pinkham, Weittenhiller, Faso, & Simpson, 2016) and review (Sasson, Pinkham, Carpenter, & Belger, 2011) papers, about the possibility of different mechanisms within ASD and SCZ producing similar behavioral outcomes. Additionally, although Crespi cites several studies suggesting divergent neurobiological mechanisms of social cognitive ability within ASD and SCZ, we are aware of several other studies, uncited in his letter, that suggest shared mechanisms (e.g. Chen et al., 2017; Ciaramidaro et al., 2018; Pinkham, Hopfinger, Pelphrey, Piven, & Penn, 2008) and several others that report both areas of neurobiological overlap and discrepancy (e.g. Cheung et al., 2010; Sugranyes, Kyriakopoulos, Corrigall, Taylor, & Frangou, 2011). Such mixed findings may emerge because of sample and methodological differences, or more likely, because some combination of shared and divergent mechanisms underlies social cognitive impairment in ASD and SCZ. We believe that the evaluation of each of these possibilities first requires rigorous, well-powered comparisons that firmly establish behavioral patterns. We hope that our paper provides this, and can be used as a roadmap for investigating mechanisms and guiding treatment.

Crespi also argues that without information on mechanism, knowledge of quantitative levels of deficits is limited in its utility. In our view, this depends on the question one is attempting to answer. As we note in the article, previous findings regarding the degree of overlap in social cognitive performance between disorders have been mixed and hampered by differences between studies that introduce confounds and preclude definitive conclusions. Our goal was to add clarity to this literature by assessing a large, well-characterized, demographically, and intellectually comparable sample of ASD, SCZ, and typically-developing participants using a broad battery of psychometrically-validated social cognitive tasks spanning a range of subdomains (e.g. emotion processing and theory of mind). By doing so, we are able to provide strong evidence that social cognitive impairments are an integral part of both disorders that should be considered when assessing prognosis, support needs, and treatment. Further, unlike many previous comparative studies, our comparison was not conducted on a single social cognitive task but rather on a comprehensive battery, and is the first to administer tasks validated for use in both ASD (Morrison et al., 2019) and SCZ (Pinkham, Penn, Green, & Harvey, 2015). Our findings therefore provide some of the strongest evidence yet that social cognitive impairment in both ASD and SCZ is not relegated to a specific area of social cognition (e.g. theory of mind) but is expansive and encompassing. Finally, as noted in the paper, we did predict specific patterns of social cognitive differences in ASD and SCZ that largely were not supported by our findings. Although we would never characterize our results as definitive, we do believe our study

to be the most rigorous social cognitive comparison of ASD and SCZ to date and feel strongly that sharing these results, regardless of whether they align with *a priori* hypotheses, is important for the field to have and use to inform future investigations.

Second, Crespi notes that diagnosis-based approaches like ours are counter to RDoC principles, and that identification of shared mechanisms is better done through investigations of how 'biological adaptations connect to psychological maladaptations.' This issue is one concerning the value of different starting points (e.g. whether investigations should be bottom-up or top-down), and we believe both offer value and depend largely on one's research questions and aims. Although it is undoubtedly helpful to examine genes and brain function in ASD and SCZ to determine how these factors relate to social functioning, behavioral comparative studies can help identify candidate genetic and neural mechanisms and provide the necessary foundation for these examinations. For example, given that social cognition is impaired in ASD and SCZ, it makes sense to investigate the functioning of social cognitive neural networks, which many studies have done. However, without these basic behavioral studies, the search for neurobiological mechanisms becomes like the search for a needle in a haystack, where we run the risk of unfocused studies that are more likely to suffer Type I error. Thus, identifying areas of behavioral overlap can help cull where within the haystack to look. Further, starting with behavioral patterns also has an important practical benefit. It is much easier and economically viable to screen individuals for social cognitive impairments and to then assess associated brain function than it is to screen for abnormal temporal parietal junction or amygdala functioning, for example, and only then test for poor social cognitive performance. Additionally, starting at the behavioral level can help identify meaningful clinical subgroups, such as SCZ patients with and without paranoia, that may help uncover distinguishing mechanisms [e.g. hypermentalizing in SCZ may be specific to those individuals who also experience paranoia (Ciaramidaro et al., 2015; Frith & Corcoran, 1996)]. In general, we believe that future studies that focus on accounting for heterogeneity within disorders (e.g. Pu et al., 2019) will be particularly profitable for informing mechanistic understanding.

Finally, in his third point, Crespi states that behavioral tasks that do not show differences between disorders cannot aid in differential diagnosis and that measures will only be helpful to the degree that they indicate differences rather than quantify deficits. The point regarding differential diagnosis is valid; however, behavioral tasks, whether they show differences between disorders or not, are essential to identifying problem areas and developing individualized treatment protocols. At the beginning of his commentary, Crespi asks what is learned by noting that someone has deficits in social cognition. Quite simply, that person and his provider have learned that he has difficulty in an area that will likely benefit from treatment. Also, because we know that there is variability in the degree of social cognitive impairment, at least within SCZ (Hajdúk, Harvey, Penn, & Pinkham, 2018), it is important to determine whether or not any individual patient is presenting with social cognitive difficulties. If the individual is functioning within the normative range, then social cognitive treatment is likely not a recommended component of treatment. Further, even in the event that treatment is warranted, we believe that one does not necessarily need to know the exact mechanism of impairment in order for treatment to provide benefit. For example, we still do not know precisely how risperidone and aripiprazole, the only FDA-approved medications for ASD, are beneficial in the treatment of both ASD and SCZ (King & Lord, 2011); yet, the lack of mechanistic understanding does not undermine their effectiveness. Similarly, Cognitive Enhancement Therapy appears to improve neurocognitive and social cognitive functioning in both ASD and SCZ (Eack et al., 2018; Hogarty et al., 2004), despite our lack of knowledge regarding the origin of these impairments. Although mechanistic understanding undoubtedly has the potential to enhance treatment benefit, the lack of clarity about underlying mechanisms existing today should not discourage or preclude individuals with social cognitive impairment from seeking out currently-available evidence-based treatments.

Thus, while it could be argued that demonstrations of divergence are more informative than demonstrations of convergence, we maintain that both are important and worthwhile. The particular benefits of identifying points of behavioral convergence are the elucidation of candidate mechanisms and the ability to reasonably explore whether mechanisms or treatments investigated in one disorder may also apply to the other. In our view, prioritizing divergence above all else jeopardizes the ability to conduct meaningful investigations. The value of studies should not be based on the presence of group differences or statistically significant findings; rather, strong and valid design should be emphasized and data taken at face value. Direct comparisons may reveal either convergence or divergence, and it would be a disservice to the field for researchers to refrain from conducting or reporting a study simply because they find similarity instead of difference.

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