COGNITION ACROSS THE PSYCHIATRIC DISORDER SPECTRUM: FROM MENTAL HEALTH TO CLINICAL DIAGNOSIS

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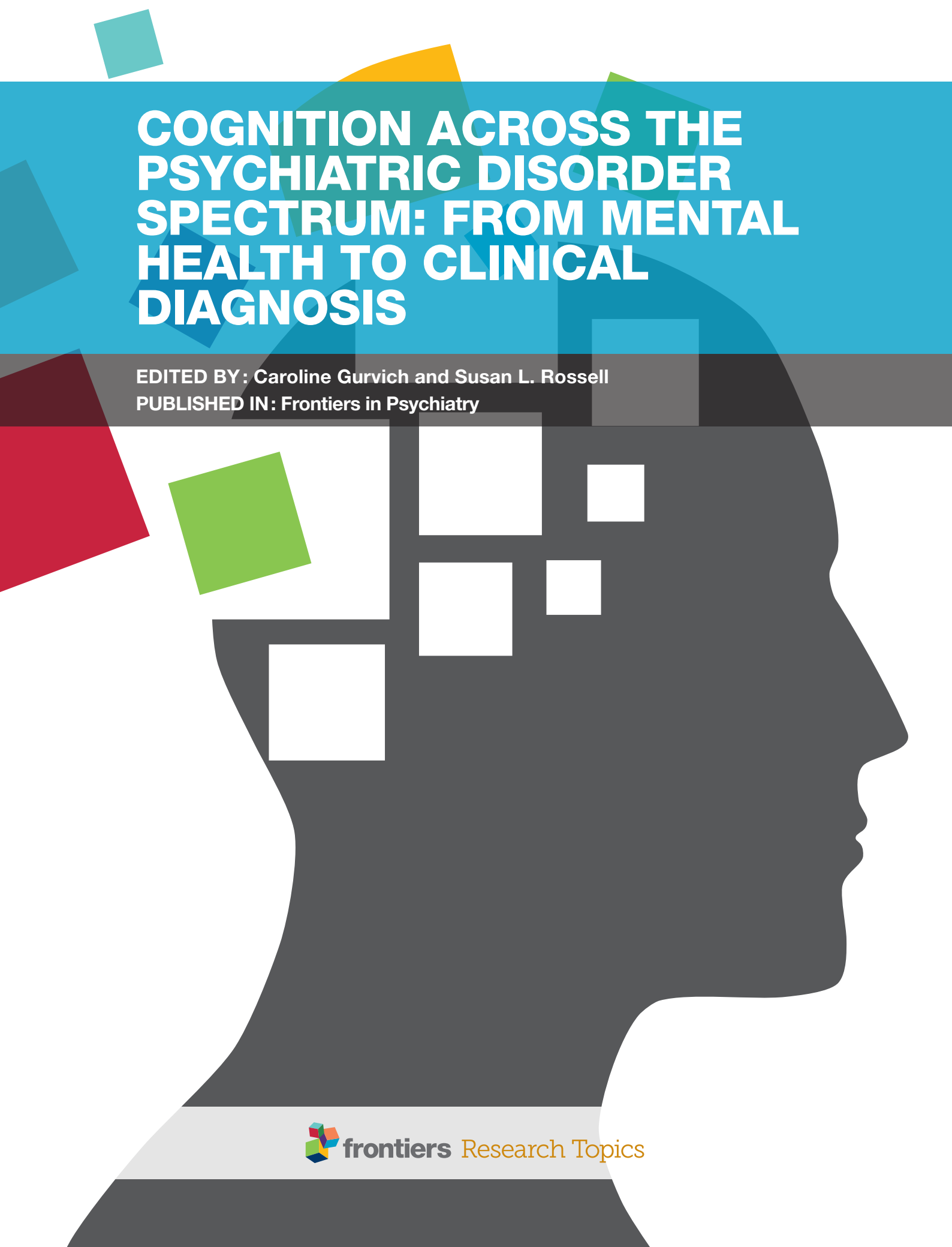

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COGNITION ACROSS THE PSYCHIATRIC DISORDER SPECTRUM: FROM MENTAL HEALTH TO CLINICAL DIAGNOSIS

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Psychiatric symptoms are considered to be distributed along a continuum, from good mental health to a diagnosable psychiatric disorder. In the case of psychosis, subclinical psychotic experiences, which can include odd behaviours, strange speech, unusual perceptual experiences and social/emotional withdrawal, are often referred to as schizotypy. Research examining schizotypal traits in non-clinical populations is rapidly expanding. The exploration of schizotypy allows us to identify areas of overlap with psychiatric disorders (schizophrenia and related disorders) at genetic, biological, environmental and psychosocial levels, thus identifying putative risk factors, as well as exploring potentially protective factors. Schizotypy is also a valuable model for exploring cognition as performance is not confounded by issues often present in schizophrenia samples, such as long-term antipsychotic medication usage, social isolation, and recurrent hospitalizations. Investigating cognition is a particularly important area of research as cognitive symptoms in schizophrenia, such as impaired attention, reduced memory and difficulties with executive functions, are a core feature of schizophrenia and strongly related to quality of life and functional outcomes, yet generally respond poorly to current treatment options.

The aim of this special Research Topic is to explore the relationship between cognition, schizotypy and the schizophrenia spectrum. The articles in this e-book draw on a variety of perspectives and represent an interesting array of opinions, reviews and empirical studies that begin to answer questions about the similarities and overlaps between schizotypy and schizophrenia spectrum disorders, contributing to our understanding of potential risk factors. Equally important is research that highlights differences between schizotypy and schizophrenia spectrum disorders that may enhance our understanding of potentially protective or adaptive features of schizotypy. Collectively, these articles highlight the exploratory potential of the study of schizotypy, particularly in relation to better understanding cognition across the schizophrenia spectrum.

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EDITORIAL
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Editorial: Cognition across the psychiatric disorder spectrum: from mental health to clinical diagnosis

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Keywords: schizotypy, schizophrenia, cognition, neurocognition, psychopathology, schizophrenia spectrum

Schizophrenia is a common psychiatric diagnosis affecting approximately 0.7% of the population worldwide (1). Cognitive symptoms in schizophrenia, such as impaired memory, poor attention/information processing, and difficulties with executive functions, are a core feature of schizophrenia and strongly related to quality of life and functional outcomes, yet generally respond poorly to current treatment options (2, 3). Further research exploring the basis of cognitive impairments in schizophrenia is essential to allow for better targeted treatment options. Improved cognition would pave a much better path to functional recovery for people with schizophrenia, for example, increasing the chances of someone being able to return to work or study when their positive psychotic symptoms are stabilized. One avenue that has emerged as a way to study symptoms of schizophrenia, such as cognition, is the study of schizotypy. Schizotypy refers to subclinical psychotic experiences (which can include odd behaviors, strange speech, unusual perceptual experiences, and social anhedonia) that are distributed along a continuum, from mental health to a diagnosable psychiatric disorder. While the term schizotypy was coined over six decades ago (4), research examining schizotypal traits in non-clinical populations has rapidly expanded over the last few years (a recent PsychInfo search of the term "schizotypy" – conducted 19/05/2015 – showed more than 5850 publications, with more than half of those publications in the last 5 years). The exploration of schizotypy may help elucidate many factors related to the etiology and development of schizophrenia spectrum psychopathology, including cognition. It is timely and important to collate current research exploring schizotypy and determine how this avenue of research can inform our understanding of cognition across the schizophrenia spectrum.

The aim of this Research Topic is to provide updated knowledge, reviews, and opinion pieces in relation to cognition, schizotypy, and the schizophrenia continuum. Drawing on a variety of perspectives and collating the results of several experimental studies will inform on the current status of schizotypy research and allow future research directions to be identified. Three key sections will be explored: schizotypy as a construct, including theoretical and methodological considerations when assessing schizotypy; a comprehensive review of dopaminergic contributions to schizotypy; and, several empirical research studies exploring cognition and symptomatology across the schizophrenia and schizotypy spectrum.

Schizotypy has been conceptualized as both taxonic/categorical and dimensional. The categorical approach (5) is based on a disease model of mental illness and considers schizotypy to be a subclinical expression of the symptoms of schizophrenia that are present in a small subgroup of the population (approximately 10%). The fully dimensional approach (6) stems from Eysenck's dimensional views of personality and describes schizotypy as continuous throughout the general population with higher levels of schizotypy, in combination with other etiological risk factors, to indicate a greater risk for developing schizophrenia. In this Research Topic, Mason (7) provides an

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interesting opinion piece that acknowledges that while there are theoretical differences between these models, both dimensional and categorical approaches may have validity and research utility in relation to schizotypy.

While the study of schizotypy is interesting in its own right (for example, as a dimension of personality), schizotypy also offers a number of advantages for studying schizophrenia liability. While many of the confounding factors associated with schizophrenia, such as hospitalization, social isolation, medication/illicit drug use, and health complications, can be controlled when using a non-clinical schizotypy population, there remain extraneous factors that should be considered when schizotypy samples are employed. Neill (8), in this Research Topic, considers some of these methodological issues, such as age, education, relative status, abuse history, and religion, when recruiting and analyzing schizotypy samples. As Neill concludes, schizotypy research is rapidly expanding and it is critical that as this field moves forward, the many potential influences on schizotypy are considered to ensure studies are well designed and statistically valid.

There is considerable evidence indicating an overlap between schizotypy and schizophrenia in relation to behavioral, cognitive, brain structure, and brain function measures. At a neurochemical level, there is a long-standing literature linking dopamine to the pathophysiology of schizophrenia (9, 10) and an accumulating literature indicating a role for dopamine in schizotypy. In this Research Topic, Mohr and Ettinger (11) review the association between dopamine, schizotypy, and cognition across a wide range of methods, including experimental pharmacological challenge studies, dopamine-sensitive cognitive and behavioral measures, molecular studies of genes that involve dopamine transmission, and molecular imaging studies of the dopamine system. The authors conclude that there is some evidence of an association between altered dopamine neurotransmission and schizotypy, particularly positive schizotypy. Importantly, the authors provide suggestions for future avenues of research that will inform neurobiological and cognitive models of the schizophrenia spectrum, paving the way for potential neuropharmacological treatments.

The second key component of this Research Topic presents several empirical studies exploring different aspects of cognition and symptomatology across the schizophrenia/schizotypy continuum.

There is a long history of experimental paradigms that attempt to induce psychotic-like experiences (such as perceptual disturbances, paranoia, and anhedonia), many of these involving various means of sensory deprivation. The effects of brief sensory deprivation and the associated experience of psychotic-like experiences are explored in this Research Topic by Daniel et al. (12) in relation to schizotypal traits (high- vs. low-hallucination proneness). The study findings indicate that sensory deprivation can be a useful, non-pharmacological tool for temporarily inducing psychotic-like states across all individuals, with schizotypal traits relating to greater levels of perceptual distortions.

The multidimensionality of schizotypy is addressed in several studies in this Research Topic. Ford and Crewther (13) explore shared phenotypes across the autism and schizophrenia spectrum disorders. They conducted a factor analysis on items from the autism spectrum quotient (AQ) and the schizotypal personality questionnaire (SPQ) in a non-clinical population. Results revealed a social disorganization phenotype common to both schizotypy and autism, as well as factors specific to both spectrums of personality.

Two studies are presented that explore the link between schizotypy and neurocognition. Louise et al. (14) investigate neurocognition and schizotypy subtypes or factors using the Oxford-Liverpool inventory of feelings and experiences (O-LIFE) in an adult community sample that accounted for psychiatric illness and family history; and hence, allowing for the exploration of both cognitive functioning and potential compensatory mechanisms in individuals who have passed the peak onset times for developing schizophrenia. Results indicated a positive relationship between poorer inhibitory control and the schizotypy factors of positive schizotypy, cognitive disorganization, and impulsive non-conformity, as well as a positive relationship between negative schizotypy and poorer attention/processing speed and reasoning and problem-solving capacity. Herzig et al. (15), in this Research Topic, explore neurocognition and schizotypy, with their primary focus being how substance use attenuates cognition. In their university-aged sample, Herzig et al. found a trend toward higher positive schizotypy scores in their "cannabis users" group (as compared to the non-cannabis users). In relation to the three cognitive tasks that they assessed (verbal short-term recall, trail-making task, and two-back working memory task), they failed to find a relationship between schizotypy scores and cognition, but found enhanced cannabis use predicted decreased verbal short-term memory, whereas enhanced alcohol use predicted reduced working memory performance. These results highlight the potential importance of controlling for substance use when exploring the links between schizotypy and cognition.

An interesting study assessing the integrity of body representations in individuals with schizophrenia is presented by Graham et al. (16), with their focus on passivity symptoms (i.e., the belief that one's thoughts or actions are controlled by an external agent). Their results highlight self-abnormalities in schizophrenia and provide evidence for both stable trait abnormalities and state changes that depend on passivity symptom profiles. Batty et al. (17) explore neurophysiological correlates of face processing in schizotypy. Their results suggest that high schizotypes (as measured by the cognitive disorganization factor of the O-LIFE) demonstrate neurophysiological anomalies relating to the early, configural stages of face processing (N170 component), a finding that has been demonstrated in schizophrenia samples. As the authors discuss, the high schizotypal group demonstrated intact behavioral performance indicating anomalies in neural processes during the earlier stages of face processing are possibly corrected during the later stages of processing.

Within the framework of the dimensional model of schizotypy, high levels of schizotypy are not necessarily pathological but possibly beneficial, particularly in relation to positive schizotypy (18). For example, there is much research positing a link between high schizotypy and the socially valued cognitive attribute of creativity [e.g., Ref. (18, 19)]. In this Research Topic, Grant et al. (20) explore the interactions between positive schizotypy and verbal intelligence in relation to stimulus ambiguity and false-positive errors. The findings from Grant et al.'s study indicate that both state and trait positive schizotypy explain much of the variance in the production of false-positive errors/stimulus ambiguity

(or by inference, hallucinatory experiences) and verbal intelligence moderates the relationship between schizotypy and the production of false-positive perceptions of ambiguous stimuli.

In relation to potential interventions across the psychosis spectrum, Lim and Gleeson (21), in this Research Topic, explore the link between loneliness and the psychosis spectrum. The authors highlight the growing interest in the relationship between loneliness and mental health disorders; and note that the more specific, and crucial, relationship between loneliness and psychotic disorders has been overlooked. A well-designed intervention to target loneliness for individuals with psychosis is warranted and may even reduce the risk of developing psychosis or experiencing a relapse of psychotic symptoms. Lim and Gleeson provide helpful guidelines to move this area of research forward.

To conclude, the articles in this Research Topic represent an interesting array of opinions, reviews, and empirical studies that contribute to the study of schizotypy. Collectively, they highlight the heuristic potential of the study of schizotypy, particularly in relation to better understanding cognition across the schizophrenia spectrum.

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OPINION ARTICLE
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The duality of schizotypy: is it both dimensional and categorical?

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Schizotypy is the notion that schizophrenia-like features can form, in the absence of illness, a temperamental "type" or personality trait. Both typological and characterological accounts were present at the notion's conception as, historically, both categorical ("Kraepelinian") and dimensional [e.g., Kretchmer's "schizothymic" temperament; (1)] accounts of psychotic illness have vied against one another with the former clearly ascendant in biological psychiatry at least. Paul Meehl's influential development of the categorical account (2) theorized the "schizotype" as the category as the fundamental phenotypic foundation of "true" schizophrenia. Variants of this model remain central to theorizing in the North American tradition at least. The dimensional view, revitalized by Hans Eysenck, is best represented in contemporary theory by Gordon Claridge's "quasi-dimensional" model (3).

In 1995, Adrian Raine and Todd Lencz (4) set out some of the theoretical and conceptual issues in schizotypal personality research and outlined the "categories versus dimensions" issue as "perhaps the most important" of all (p. 5). They suggested pursuing both approaches so as to see, which is most productive. There is of course a distinction here between *theory* and *methodology*. I aim to argue here based on four observations of the empirical literature that aspects of *both* theoretical accounts may be valid, and that a diversity of methods may have utility in the field.

Claridge's dimensional account postulates *underlying* dimensionality of risk for illness with superimposed clinical discontinuities – the schizophrenic "spectrum" of illnesses. The critical difference between the two accounts of schizotypy lies in the non-clinical portion of the phenotype. In the categorical account, only a portion of phenotypic schizotypy is at genuine elevated risk, the "true" schizotype, the remainder is pseudophenotypic, superficially mimicking schizotypy but not possessing true genetic risk: Adrian Raine (5) termed the latter "pseudo-schizotypal." In the dimensional account, by contrast, there is the possibility of "genuine" schizotypy possessing a healthy or adaptive outcome (6); a theme I reprise in my conclusions.

A few years ago (7), I conducted a bibliographic analysis of the schizotypy literature that evidenced the growing popularity of empirical research in the field (schizotyp* OR schizoid* OR psychosis prone*), and of experimental studies in particular. In addition, I divided the empirical literature into psychometric and experimental studies, and into those taking a categorical and dimensional approach (based on their statistical treatment). The major growth in the literature has been in experimental studies of which more have taken a dimensional (e.g., correlational) approach (**Figure 1**).

Clearly, there are advantages and disadvantages to both statistical approaches and this choice does not necessarily imply a strong theoretical preference. For example, most quantitative genetic studies examine correlations as a matter of course. Conversely, studies based on diagnostic procedures usually retain a categorical approach. Moreover, a minority of studies report both statistical treatments, often with broadly commensurate results. Treating schizotypy variables as continuous variables is perhaps sometimes preferred as statistical power in many analyses is likely to exceed dichotomized treatment. This is especially the case if the latter takes seriously the taxonomic prediction of 10–15% of a general population sample (arguably a "median split" is the worst of all possible worlds). Large samples are required if the truly taxonomic approach is to be taken in a multivariate analysis. While this suits some fields such as quantitative genetics, it is not suited to others such as brain imaging. On the other hand, a common strategy is to preselect "schizotypal" and "non-schizotypal" groups via large-scale screening using a psychometric instrument. This usefully reduces the number needed to test experimentally to achieve statistical power. However, the strategy may or may not imply testing of a categorical model – it is also, of course, a strategy of convenience for testing dimensional differences.

As a consequence of all these considerations, I would argue that while genuine differences clearly exist between the models theoretically, these are very rarely tested against one another genuinely at the empirical level. Evidence can be found (and is often rehearsed) for both categorical and dimensional positions – even from the same dataset. In some ways, this apparent duality may parallel the famous "wave–particle" duality of quantum theory that suggests that both accounts can be "true" in different ways, and thus seeks to explain a diverse range of observations. At the crudest level, one can observe that broad measurement of trait tendencies tend to produce continua, and narrow "symptom-focused" measures lead to categories. I would like to suggest some important ways that *both* may have validity and research

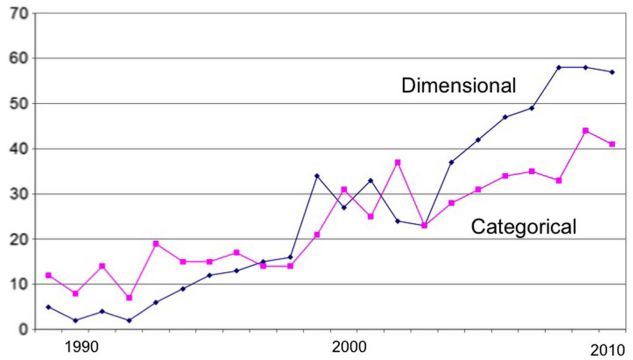

FIGURE 1 | Bibliometrics: dimensional and categorical approaches.

utility (and I do not claim that this is an exhaustive list).

I am not alone in noticing empirical evidence for both positions (8). From reviews of the epidemiological evidence of clinical disorders, Linscott and van Os suggest that there is true continuum to the non-clinical. Where I differ from their position is their suggestion that evidence in the general population suggests a latent categorical structure with "two types of people." This structure is generally argued for as a result of attempts to identify a taxon psychometrically. However, the statistical issues of this argument certainly allow for divergent interpretations: the issue of taxonometrics in schizotypy has been much discussed with little resolution (e.g., see Personality and Individual Differences 44:8; 2008). Where I do agree with their position is in viewing schizotypy *per se* as too narrow a lens, "psychosis proneness" captures the variety of traits relevant to psychotic disorders as a whole.

TRAIT MULTI-DIMENSIONALITY

Regardless of psychometric arguments about putative taxons, it is likely that some measures suit one theoretical position better than another. Those with "stronger" symptom-like measures may tend to discontinuities, while others offer greater dimensionality. In addition, even the range and nature of dimensions of schizotypal personality are argued over, with perhaps the broadest consensus concerning a distinction between positive and negative schizotypy. Arguably, there are stronger indications for the taxonomic nature of negative schizotypal features such as trait anhedonia [for review see Ref. (9)]. Conversely, Edens et al. (10) found "compelling evidence in two studies of a latent dimensional structure to paranoid traits." In general, and perhaps somewhat surprisingly, there is better evidence for the continuous distribution of "positive" schizotypy (e.g., delusional/paranoid ideation and hallucination proneness) than for "negative" schizotypy (anhedonia/social impairment).

THE POTENTIAL UTILITY OF SCHIZOTYPAL CLUSTERS

In a development of this first point, Suhr and Spitznagel (11, 12) attempted to overcome the common inconsistency of neurocognitive findings in schizotypy by clustering schizotypal individuals rather than studying individual dimensions. Executive function deficits were selectively seen in the negative schizotypy cluster; who were also more often rated neurocognitively impaired. However, a cluster high on both positive and negative schizotypy had the most unusual social behavior ratings. Subsequently, Barrantes-Vidal et al. (13) similarly advanced evidence that clusters worked more effectively than dimensions in predicting neurocognition and neurological "soft signs." Arguably, the confluence of dimensional traits to produce a "taxon-like" cluster may be best suited to identifying those with neurocognitive deficits, and possibly also in other experimental contexts.

THE OPERATION OF DISCONTINUOUS "STATE-LIKE" PHENOMENA

While personality traits are usually seen as broadly consistent over time, stress or other unusual circumstances produce "state" effects that may possess qualitatively different, and thus discontinuous, features. In this way, traits may proceed, more or less temporarily, to "symptoms" in the absence of a diagnosed syndrome. Usually these are probably highly temporary, but where more persistent or frequent that they effectively form sub-syndromal versions of disorders such as "basic symptoms" captured by the Schizophrenia Proneness Instrument (14). These sub-syndromal symptoms may be associated with the more clearly dysfunctional cognitive, affective, and behavioral features of schizotypy/schizophrenia. As they can become quite persistent states, they may well give the appearance of a taxon.

EPISTATIC MECHANISMS MEDIATING GENE–ENVIRONMENT INTERACTION

It is increasingly accepted that many individual loci each make a very small contribution to overall genetic risk (15). On *prima facie* grounds, such evidence supports the notion of one or more continua (16, 17) and probably underpins the heritability seen for broadly defined schizotypal traits. However, there remains the possibility for individual schizotypal features to arise from more specific gene loci, or more likely from complex gene-gene and gene-environment interactions. Overall, it is difficult to disambiguate continuous from discontinuous genetic effects from studies of heritability alone. One of the largest heritability studies to date (18), albeit with no single standard psychometric scale, suggested a pattern of heritability for social anhedonia consistent with a single dominant gene as postulated in the Meehlian account. Overall, many heritability studies [e.g., Ref. (19)] postulate heritability of around 50% with the remainder due to non-shared environmental variance. While the quest for a "schizophrenia gene" able to discriminate clinical from non-clinical groups continues with linkage and genome-wide association studies, there has been little sustained success: Weinberger concluded that results "are decidedly disappointing to those expecting this strategy to yield conclusive evidence of common variants predicting risk for schizophrenia" [p. 840, Ref. (20)]. A small number of gene-of-interest (GOI) studies have nevertheless some consistent results

largely with positive schizotypy. These concern the polymorphisms of genes relevant to dopamine transmission such as COMT (16, 21), DRD1 and DRD2 (22), SLC6A3 (16, 21), or MAOA (16). Such studies evidence greater schizotypy associating with several polymorphisms such as rs4680 SNP (single nucleotide polymorphisms) within the COMT-gene in a continuous fashion. However, sometimes this association is only seen in the presence of an environmental factor such as childhood abuse (23). As investigation of these in detail is in its infancy, it is likely that much greater specification of their relevance and mode of action will occur in future studies.

There is also increasing evidence of epigenetic action, whereby environmental factors influence the expression of genes (15, 24). Svarkic et al. [p. 2, Ref. (25)] outline a model, whereby "abnormal epigenetic states with large effects are superimposed on a polygenic liability to schizophrenia." This is effectively an extension or variant of point 3 and highlights how the actions of specific genes (individually making a small quantitative contribution to risk) may translate into genuinely taxonomic discontinuities – *but only in the context of a pathogenic environment.*

CONCLUSION

Overall, I have attempted to argue that *even in the non-pathological* domain of schizotypal individual differences there are numerous possibilities for both dimensional and categorical expressions both of traits and states. Taxonomic expression has greater support for negative schizotypal features such as anhedonia and potentially some associated neurocognitive features; positive schizotypy, on the other hand, sees much empirical support for "true" dimensionality at both genotype and phenotypic expression. Even here, however, there is room for gene–environment interactions and epigenetics to produce discontinuous results.

As a rider to this final point, it is apposite to point out that there may equally be important phenotypic consequences for schizotypy in the absence of a pathogenic environment or the presence of a protective factor such as high cognitive or emotional intelligence. Thus, positive schizotypy is also associated with a range of "healthy" or at least adaptive outcomes. Again, paralleling the advantages seen with cluster analytic approaches, Tabak and Weisman de Mamani (26) identified several schizotypal latent profiles: the negative/disorganized schizotypy profile had the poorest levels of well-being and schizotypes solely with positive features had the highest – commensurate with non-schizotypes. Taking a similar latent profile analytic approach to a non-clinical sample, Hori et al. (27) described 15% as "high-positive-schizotypy/adaptive" and possessing of high self-directedness, cooperativeness, and self-transcendence. This is consistent with growing evidence of the highly creative and spiritual outcomes for some schizotypal individuals (28, 29), and may point to the operation of antagonistic pleiotropy or genetic linkage such that schizotypal traits survived throughout our evolutionary history (30).

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Methodological considerations in the recruitment and analysis of schizotypy samples

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The schizotypy analog allows researchers to control for many of the confounding factors associated with schizophrenia (e.g., medication/illicit drug use and health complications) (1–3). There are, however, still extraneous factors that should be considered when schizotypy samples are employed. The purpose of this article is to highlight some of the areas of consideration including age, education, relative status, abuse history, and religion.

AGE AND EDUCATION

Most schizotypy studies recruit undergraduate students between the ages of 18–24 years (4–10). The ease with which researchers can access students makes this an attractive option, especially when large samples can be drawn upon from which "high schizotypy" individuals can be sourced. There are, however, well-documented problems with this approach. The age old argument of whether university student performance can be generalized to the population must be considered (11), particularly when the samples are drawn specifically from first-year psychology students. Despite these concerns, there is some evidence that older samples (mean age 40 years) do not necessarily score differently from younger university samples (12). Further research into the effect of education is required; the effects of age are examined next.

SCHIZOTYPY LEVELS OVER THE LIFESPAN

There is evidence that levels of schizotypy change as people age (13–16). Mason (16) reported that while positive schizotypy features decrease with age, introvertive anhedonia (negative symptom analog) actually increases. This may be analogous to the reported reduction in positive symptoms and increased negative symptoms seen in later stages of schizophrenia (17, 18). Thus, recruiting younger groups may result in higher schizotypy scores than would be found in older groups. These younger groups, however, may serve as an appropriate analog only for early stages of schizophrenia. It may be more appropriate to explore issues relating to chronic schizophrenia using an older schizotypy sample. Recruitment of high schizotypy from non-student populations will require a more targeted approach; one method would be to focus on creative individuals including artists and musicians (12) as schizotypy levels are often higher among those in more creative or artistic positions.

RELATIVE STATUS

Evidence suggests that schizotypy is higher among relatives of those with psychosis than it is in the general population (19). Studies including relatives have reported that within their high schizotypy groups, schizotypy levels are higher and more variable among those who are relatives (20, 21). Given the difference in performance among relatives, future studies should consider examining relatives separately or at least reporting the breakdown of relatives versus non-relatives among their samples.

HISTORY OF TRAUMA

There is a relationship between physical or sexual abuse and the development of psychosis with some authors going so far as to describe the relationship as "causal" (22). This same relationship has been found in the schizotypy literature (23). Further, evidence suggests that such trauma is associated with the development of specific psychosis symptoms, namely hallucinations (24, 25). Given that the development of specific symptoms has been related to trauma, the same suggestions put forward for relative status (separate analysis for those with a trauma history/report breakdown of trauma vs. non-trauma) should be considered for trauma.

RELIGION

Religion is a complex area of investigation in psychosis research. It can be difficult to tease apart delusions with religious content from "healthy" religious belief. This distinction can be even more complicated when examining the schizotypy continuum. In the search for pathology indicators, researchers have noted higher levels of schizotypy among those associated with new religious movements (Hare Krishnas and Druids) compared to levels found among those following mainstream religions (Christianity) (26). Other research has found that religious preoccupation relates to high schizotypy (27). It may be that an association with less mainstream religion and preoccupation may serve as signifiers of more pathological religious belief, which may link to schizotypy. Future research should investigate the relationship between religion and current schizotypy scales to determine whether healthy and more pathological beliefs of a religious nature are contributing to schizotypy scores. Further, those

studies that have investigated schizotypy and religion find a gender effect, which should also be considered (27, 28). With one study finding the link between religion and schizotypy only existed for the males in their sample (27). Another paper found that religion related to different aspects of schizotypy depending on gender with men demonstrating a relationship between intrinsic orientation toward religion and more borderline features of schizotypy while for women, there was a relationship between social orientation in religion and paranoia and borderline features (28).

DICHOTOMIZING CONTINUOUS MEASURES OF SCHIZOTYPY

In the schizotypy literature, many authors opt to do median splits of their participants to create a "low" and a "high" schizotypy group. This topic will be discussed in more detail in this issue by Mason. As such, this piece will summarize only the main concerns associated with this approach. Firstly, dichotomizing the data results in a loss of power with estimates suggesting that dichotomizing equates to a loss of a third of the data (29). Further, using this method can increase both type I (based on the reduced power) (30) and type II errors (especially when "optimal" or "minimum p value" approaches are taken) (31). Further, it appears that dichotomizing data is more problematic than splitting the sample into more than two groups. Non-linear, especially *U*-shaped relationships, are generally lost using a median split but might be seen if more than two groups are formed (29, 32). Some studies choose to use the upper and lower thirds or top and bottom 25% of their samples to split their groups (33, 34) including one of my own studies: (35). This creates an additional problem, namely, the "low" group. It does not seem likely that the low group is actually representative of the general population. In fact, researchers have suggested that very low scores on the O-LIFE might reflect a tendency to more autistic traits (36). Researchers should consider these significant problems when determining whether to split their data.

CONCLUSION

Schizotypy research has been conducted for many years; however, this field is still in its infancy compared to the schizophrenia research field. This area of study is increasing and as such, it is our responsibility to ensure that our research considers the influence of some of the underlying contributions to scores (genetics and trauma) as well as some of the complications, which are often overlooked in the schizophrenia literature (role of religion) as well as ensuring that our studies are well designed and statistically valid.

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An overview of the association between schizotypy and dopamine

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Schizotypy refers to a constellation of personality traits that are believed to mirror the subclinical expression of schizophrenia in the general population. Evidence from pharmacological studies indicates that dopamine (DA) is involved in the etiology of schizophrenia. Based on the assumption of a continuum between schizophrenia and schizotypy, researchers have begun investigating the association between DA and schizotypy using a wide range of methods. In this article, we review published studies on this association from the following areas of work: (1) experimental investigations of the interactive effects of dopaminergic challenges and schizotypy on cognition, motor control, and behavior (2), dopaminergically supported cognitive functions (3), studies of associations between schizotypy and polymorphisms in genes involved in dopaminergic neurotransmission, and (4) molecular imaging studies of the association between schizotypy and markers of the DA system. Together, data from these lines of evidence suggest that DA is important to the expression and experience of schizotypy and associated behavioral biases. An important observation is that the experimental designs, methods, and manipulations used in this research are highly heterogeneous. Future studies are required to replicate individual observations, to enlighten the link between DA and different schizotypy dimensions (positive, negative, cognitive disorganization), and to guide the search for solid DA-sensitive behavioral markers. Such studies are important in order to clarify inconsistencies between studies. More work is also needed to identify differences between dopaminergic alterations in schizotypy compared to the dysfunctions observed in schizophrenia.

Keywords: schizotypy, personality, dopamine, cognition, psychopharmacology, neuroimaging, genetics

INTRODUCTION

Schizotypy, first coined by Rado (1), is a set of personality traits thought to mirror the subclinical expression of schizophrenia in the general population. Schizotypy encompasses behaviors, cognitions, and emotions resembling the signs and symptoms of schizophrenia. It is typically assessed in the general population using psychometric self-report questionnaires including, among others, the Schizotypal Personality Questionnaire (SPQ) (2), the Oxford–Liverpool Inventory of Feelings and Experiences (O-LIFE) (3), the Chapman scales (4), and the Rust Inventory of Schizotypal Cognitions (RISC) (5). Factor analytic studies have shown that schizotypy consists broadly of three subdimensions (3, 6). The *positive* schizotypy dimension describes perceptual aberrations resembling the hallucinations of schizophrenia as well as unusual views and ideas resembling the delusions of schizophrenia. The *negative* schizotypy dimension describes a loss of normal emotional, physical, and social functions such as the experience of pleasure or interest in social contacts. Finally, the *disorganized* dimension encompasses eccentric behavior and odd speech. Overall, the symptomatic phenomenology of schizotypy thus resembles the factor structure of symptoms reported in schizophrenia (7).

The literature tends to draw upon two scientific approaches toward the study of schizotypy, i.e., the quasi-dimensional and fully dimensional approaches. The quasi-dimensional, psychiatrically oriented approach, proposed by Meehl (8, 9), regards schizotypy as the subclinical expression of the symptoms of schizophrenia (10, 11). In that approach, schizotypal individuals are hypothesized to carry the genetic risk for schizophrenia. Evidence for this approach stems from some (12), but not all (13), taxometric studies. The fully dimensional approach (14), championed by Eysenck and Claridge (13, 15–18), regards schizotypy as a personality trait which is continuously distributed. It is assumed that schizotypal symptoms in the healthy population are qualitatively similar though quantitatively milder than those observed in schizophrenia. Evidence for the fully dimensional approach stems from taxometric studies that consider positive skewness of sample distribution (13). The high prevalence of psychotic-like experiences in the general population is also in accordance with the fully dimensional approach (19, 20). Importantly, both approaches emphasize the observation of variation in schizotypal features in the population. More work is, however, needed on the exact nature of the distribution and the boundary between non-clinical schizotypy and clinical schizophrenia (12, 13, 21, 22).

Irrespective of these open psychometric questions, biopsychological research on schizotypy is also based on the continuum assumption. There is considerable evidence that behavioral and

brain correlates of schizophrenia are also related to schizotypy [for review, see, e.g., Ref. (11, 23, 24)]. By and large, the focus of these schizotypy studies has been on behavioral, cognitive, brain structural, and brain functional measures. Neuronal information transfer is, however, only possible with functional neurochemical transmissions at synapses. Therefore, neurochemical studies involving pharmacological challenges or molecular imaging methods are of utmost importance for our understanding of schizotypy. Most prominent so far are studies that link schizotypy to dopamine (DA). Comparable to above mentioned study domains, this link originates in the continuum assumption because schizophrenia has been linked to DA (25, 26), schizotypy might be associated with DA as well. In the following, we will explore this possible link. We will describe a selection of relevant psychopharmacological studies in patients with schizophrenia before referring to schizotypy studies that test the possible link to DA. First, however, we briefly introduce the structure and function of the DA system.

At this point, it should be mentioned that the schizophrenia spectrum also of course includes individuals with schizotypal personality disorder (SPD) and those at increased genetic or clinical risk for the illness. However, in the interest of focus, we restrict this overview to psychometrically identified schizotypy. Of course, it should be acknowledged that some, but not all, individuals with high levels of schizotypy also qualify for a diagnosis of SPD. For example, Raine (2) observed SPD in 55% of participants with SPQ scores in the top 10% of the distribution.

THE STRUCTURE AND FUNCTION OF HUMAN DOPAMINE SYSTEMS

Neurotransmitters exert different actions throughout the brain; the type of action depends on the neurotransmitter, action site, and/or neuronal circuit (27). For instance, the amino acids GABA (inhibitory) and glutamate (excitatory) are found throughout the brain. Acetylcholine and monoamines (DA, norepinephrine, serotonin), on the other hand, are organized in systems. Systems imply that cell bodies producing these substances are located subcortically in anatomically circumscribed regions (27). In the case of DA, the nigrostriatal (important to motor control), mesolimbic (important to reward and motivation), and mesocortical (important to prefrontal functions) pathways have been distinguished on the basis of where their cell bodies are located and where their axons project. Moreover, two major DA receptor families have been identified, viz. the D1-like (D1 and D5) and D2-like (D2, D3, D4) receptors that are widely distributed throughout the brain. Because of the importance of the DA system to various mental health conditions, its complexity and functioning remain intensively investigated (28).

Of course, complex mental health disorders cannot be explained by single changes to complex neurotransmitter systems. Instead, subsystems are likely contributors to different psychopathologies. DA has indeed been associated with diverse neurological and psychiatric conditions such as Parkinson's disease, schizophrenia, addiction, and attention deficit hyperactivity disorder [e.g., Ref. (29, 30)]. Also, neurotransmitter systems are not modular, i.e., they do not exert their actions in isolation. A given neurotransmitter system is in constant interaction with other systems. In schizophrenia, interactions between the DA and glutamate systems are intensively debated (31). Accordingly, pharmacological compounds can enhance DA release while also enhancing the release of the other two monoamines (norepinephrine, serotonin). The latter release might happen directly or indirectly through metabolism of DA into norepinephrine and the latter into serotonin (32, 33). This overall complexity in neurotransmitter systems highlights the fact that individual psychopharmacological studies have inherent limitations in investigating the link between schizotypy and DA. As exemplified in the following sections, we depend on findings from a multitude of studies using different but complementary approaches.

DOPAMINERGIC EFFECTS IN PATIENTS WITH SCHIZOPHRENIA

Neuroleptics were first discovered in the early 1950s (34). Since their discovery, it has been shown that these DA antagonists ameliorate acute psychotic symptoms [e.g., Ref. (35, 36)]. It is still accepted that DA is key in the treatment and pathophysiology of schizophrenia (37–39). For example, patients with schizophrenia profit from DA antagonistic treatment (38) and show symptom worsening after DA agonistic treatment (40, 41). In healthy populations, DA agonists can trigger psychotic or psychosis-like symptoms (42, 43). Such findings led to the suggestion that a hyperactive DA system results in acute psychotic symptoms (25, 38). Davis et al. (25) further elaborated on this suggestion by proposing DA abnormalities to depend on the brain region, i.e., D1 receptors being predominantly found cortically and D2 receptors subcortically. They specified that frontal hypodopaminergia would result in striatal hyperdopaminergia. Regarding symptoms, they related negative symptoms to frontal hypodopaminergia and positive symptoms to striatal hyperdopaminergia.

Howes and Kapur (44) refined this previous DA theory by suggesting that multiple "hits" (e.g., social, environmental, and cultural stressors) result in DA dysregulation at the pre-synaptic level. Such DA dysregulation is hypothesized to lead to changes in how events are appraised, potentially because events become overly salient (i.e., attract increased allocation of meaning). According to these authors, an alteration in pre-synaptic DA is the final common pathway to psychosis and psychosis-proneness (45). Yet, other evidence points to the role of post-synaptic processes (46). Very recently, Seeman (39) outlined how dynamic changes of post-synaptic D2 receptors might contribute to symptoms experienced in schizophrenia. Mainly based on animal studies, Seeman reports on D2 receptors that can either take a high affinity state for DA (D2High) or a low affinity state for DA (D2Low). Reviewing the literature, he suggests that psychosis is associated with the more active and normally less common D2High state.

Overall, despite various suggestions on the involvement of alternative neurotransmitter systems in psychosis and, by inference, schizophrenia (31, 47), recent notions highlight that DA is the likely final common pathway to psychosis. The precise mechanisms and sites of action remain inconclusive, and continued research reveals ever more complex synaptic dynamics such as the ones described for the D2High and D2Low affinity states. It remains to be clarified whether such alterations of the DA system are specific to overt clinical psychosis or are also evident, though less pronounced, along the schizophrenia spectrum

including healthy schizotypy. Howes and Kapur (44) previously reviewed a number of studies showing an involvement of DA in the prodromal state, in ultra-high risk populations, in relatives of schizophrenia patients and in schizotypy. Because these populations lie on the psychosis continuum, part of these and additional studies will be discussed in more detail.

In an 18F-dopa positron emission tomography (PET) study, Howes et al. (48) observed that patients with prodromal psychotic symptoms showed enhanced striatal 18F-dopa uptake, intermediate to that of patients with schizophrenia and healthy controls. This enhanced uptake correlated positively with prodromal symptomatology and neuropsychological impairments [but see in Ref. (49)]. In a 3-year follow-up study, Howes et al. (50) observed that greater striatal DA synthesis capacity was observed in a psychosis transition group as compared to a group that did not transit into psychosis. Moreover, this capacity in the transition group correlated positively with symptom severity. In another study, elevated pre-synaptic striatal uptake was comparable between patients with SPD and remitted patients with schizophrenia (51). It was also elevated for individuals at ultra-high risk for psychosis, i.e., those who show impaired socio-occupational functions and attenuated psychotic symptoms (e.g., perceptual abnormalities, paranoia) (52). An increase of striatal pre-synaptic DA synthesis has also been observed in first-degree relatives of patients with schizophrenia (53). Relatives additionally showed an altered stress response, demonstrated by increased levels of plasma DA metabolites when compared to healthy controls (54). This increase was associated with psychotic-like symptoms subsequent to daily stressors (experience sampling methodology) (55). In yet another study, psychotic patients and unaffected relatives released significantly more DA in striatal regions subsequent to the inhalation of delta-9-tetrahydrocannabinol (the main psychoactive ingredient of cannabis) than healthy controls (56). In sum, these studies show that DA abnormalities are not restricted to individuals with a clinical diagnosis of schizophrenia, but are also evident in the extended phenotype. Findings specific to schizotypy are presented further below.

METHODS IN THE STUDY OF DOPAMINE AND ITS RELATION TO SCHIZOTYPY AND COGNITION

Various methods are available to measure aspects of the DA system in healthy humans. The most promising to study the link between schizotypy and DA include (1) experimental pharmacological challenges of the DA system, (2) neurobiologically informed, DA-sensitive cognitive and behavioral measures, (3) molecular studies of genes involved in DA neurotransmission, and (4) molecular neuroimaging of the DA system. Here, we briefly outline these methods. In the next section, we discuss how they have been used in work on schizotypy.

The first methodological approach directly tests the link between schizotypy and DA. For instance, one could test DA agonistic and antagonistic treatment effects on the experience of schizotypy as well as related correlates in healthy populations. This approach corresponds to tests of medication effects in patients. In patients, however, pharmacological treatment consists of the daily administration of medication over many weeks, given that the clinical antipsychotic effects of such compounds take several weeks to emerge (57). When testing healthy populations, such long-term drug administration would be unethical and potentially dangerous. For instance, antipsychotic treatment causes severe side effects [e.g., Ref. (58) for a meta-analysis]. These and other (e.g., economic and clinical) factors explain why the investigation of long-term medication effects is common in clinical studies while single (or limited) short-term drug effects are frequently investigated in healthy volunteers.

Importantly, short-term dopaminergic drug applications directly modulate the DA system, thereby allowing the evaluation of dopaminergic effects on domains of cognition, emotion, motor control and their neural correlates. Such studies tend to take place in well-controlled laboratory settings using tight methodological controls, such as double-blind procedures and placebo conditions [e.g., Ref. (59–61)]. Such paradigms inform on acute drug effects and their interaction with schizotypy. They also allow addressing clinical questions hard to implement in patients (40–43). As outlined above, however, it should be borne in mind that the DA system does not work in isolation but instead interacts with other neurotransmitter systems; therefore, the specificity of any pharmacological effect on behavior and cognition remains to be characterized further.

The second methodological approach involves the assessment of DA-mediated cognitive and behavioral performance measures and their covariance with schizotypal personality traits. This approach is indirect in comparison to the first approach. Yet, the use of DA-mediated performance measures is popular. Various paradigms have been drawn upon (62–67). Of importance, previous studies have shown that these performance measures are sensitive to modulations of the DA system. In particular, such measures are affected by dopaminergic drugs in humans [e.g., Ref. (61, 68, 69)], human mental health conditions in which the DA system is affected [e.g., Ref. (64, 65)] and by experimental dopaminergic interventions in animals [e.g., Ref. (64, 69)].

The third methodological approach involves molecular imaging methods. As indicated above, methods such as PET and single photon emission computed tomography (SPECT) can provide *in vivo* data on markers of the DA system (such as DA synthesis or receptor and transporter availability) in the human brain (45). These markers can be quantified and related directly to schizotypy scores. As will be detailed below, PET and SPECT methods have recently been applied to study the DA system as a function of schizotypy.

The fourth methodological approach involves the exploration of the role of DA in schizotypy by studying statistical associations of schizotypy scores with variants in genes whose protein products are known to be involved in the DA system (70, 71). Such genes may include those coding for receptors, transporters or enzymes involved in DA synthesis, release, reuptake, degradation or any other aspect of DA transmission. The effects on DA transmission of such genetic variants, when known, allow drawing conclusions about differences in DA transmission in relation to individual differences in schizotypy.

DOPAMINE AND SCHIZOTYPY: EMPIRICAL EVIDENCE

A role of DA in schizophrenia and schizotypy has long been postulated (67, 72–74). Empirical evidence on the nature of the

association between DA and schizotypy has been scarce and the association has rarely been investigated directly (68, 75). However, studies have accumulated over the last 15 years. Here, we give an overview on the outcome of these studies, irrespective of which methodological approach has been applied. In case that DA was investigated indirectly (the second methodological approach mentioned above), we distinguish between studies that assessed more basic behavioral functions and those that assessed higher cognitive functions. Often these studies added a direct manipulation of the DA system using the first methodological approach outlined above. Therefore, we discuss these together with the purely behavioral data on simple or complex behavioral functions. In the case of molecular genetic and molecular imaging studies, many findings are based on associations with questionnaire scores. We discuss these studies separately.

BASIC BEHAVIORAL FUNCTIONS

Turning behavior is a behavioral marker of a relatively hyperactive DA system in one over the other hemisphere. Animal studies [Ref. (76) for overview] and a study testing patients with asymmetrical Parkinson's disease (77) showed that whole-body turning occurs away from the hemisphere with the more active DA system. Acutely psychotic patients (65) and individuals with elevated positive schizotypal features (74) yielded a preference for left- over right-sided turns pointing to a relative hyperactive right-hemispheric DA system along the schizophrenia spectrum. In a study that directly tested the influence of DA on turning behavior, half of the participants received a placebo and the other half a non-specific DA agonist (levodopa) (78). Turning biases were investigated as a function of participants' positive and negative schizotypal features. The authors found that elevated positive schizotypy associated with a left- over right-sided turning preference in the placebo group. In this same group, negative schizotypy associated with a right- over left-sided turning preference. In the levodopa group, these relationships were not strengthened, but actually reversed. The authors argued that a higher than normal DA availability might have balanced out pre-existing DA asymmetries. In another experiment on the same participants, schizotypy and levodopa treatments were unrelated to lateral turning biases in a computer-based object-rotation task (66).

Spontaneous eye blink rate (SBR) is indicative of cerebral DA activity. Eye blinks occur spontaneously, frequently, and mostly without awareness. They are primarily important for the health of the eye surface and clarity of vision. Decades ago, SBR has been suggested to be a sensitive marker of striatal DA activity (64). SBR has been associated with changes in concurrent cognitive processes, perceptual load, and level of arousal (79, 80). It is enhanced in schizophrenia, in particular in the unmedicated or drug-naïve state (64, 81, 82), and decreases with antipsychotic treatment (64, 82, 83). In line with Davis et al.'s (25) notion of a link between negative symptoms and hypodopaminergia on the one hand and positive symptoms and hyperdopaminergia on the other hand, negative symptoms were associated with a decreased SBR (83) and positive symptoms with an increased SBR (82, 83). Additionally, SBR increased with a DA agonistic treatment in healthy individuals (84, 85).

In a dopaminergic challenge study, half of the participants received a placebo while the others received an unspecific DA agonist (levodopa) (86). SBR did not differ between substance groups, but correlated positively with negative (but not positive) schizotypy scores after levodopa intake. The authors conjectured that this effect occurred because negative schizotypy is *a priori* related to hypodopaminergia. In another study, however, SBR correlated positively with participants' psychoticism scores, a subdimension of the Eysenck Personality Questionnaire (87). Some authors argued that psychoticism forms part of the schizotypy spectrum (88). Other authors linked psychoticism to impulsiveness, lack of cooperation, rigidity, low superego control, low social sensitivity, low persistence, lack of anxiety, and lack of feelings of inferiority (89) – features associated with borderline and antisocial personality disorder rather than with the schizophrenia spectrum (90, 91). The psychoticism dimension seems indeed the least clear-cut dimension of the three Eysenckian dimensions (90, 91). Whatever the psychoticism dimension is measuring, the latter SBR finding suggests that psychoticism is probably more sensitive to the DA system subserving SBR than is schizotypy (or negative schizotypy) as such.

Stereotyped behavior is thought to be sensitive to DA. It is observable in schizophrenia (92, 93) and after amphetamine consumption in healthy individuals (69). In schizophrenia, stereotyped behavior occurs on the motor (e.g., walking backwards and forwards, repetitive jaw movements) (94) and higher cognitive level. For instance, perseverative errors in the Wisconsin Card Sorting Test are elevated in schizophrenia [Ref. (95) for overview], SPD (96, 97) and as a function of both high positive and negative schizotypy (98, 99). Random number generation tasks show that patients with schizophrenia (100, 101), healthy participants after amphetamine administration (69), and healthy positive schizotypal participants (102, 103) yield stereotypical response biases when compared to respective controls. Finally, when rotating figures into advantageous target positions on a computer screen, left or right turns had to be applied dynamically to obtain maximal scores (66). Sticking stereotypically to one or the other direction would be disadvantageous. The latter study reported on two experiments with one being a between-subject levodopa placebo-controlled experiment. The authors observed that individuals with relatively high as compared to low positive schizotypy were behaving more stereotypically. Yet, in the levodopa group, high positive schizotypal individuals performed less stereotypically than the low positive schizotypal individuals. Comparable to the findings on turning behavior, results seem to suggest that a higher than normal DA availability in positive schizotypes balances out pre-existing DA-mediated behavioral abnormalities.

Prepulse inhibition (PPI) is another DA-sensitive measure that has been studied in relation to schizotypy. PPI is a cross-species phenomenon that refers to a reduction in the amplitude of the startle response to a strong sensory stimulus, the pulse, if this stimulus is preceded by 30–500 ms by a weak stimulus, the prepulse (104). The weak prestimulus is thought to evoke inhibitory mechanisms, which limit further stimulation until the processing of the prepulse has been completed, resulting in a reduced impact of the pulse. PPI is thought to reflect an early sensory gating process to avoid interference from simultaneous

processing of several stimuli. It is, thus, a largely automatic measure of inhibitory function. Experimental studies in animals have shown that a cortico-striato-pallido-thalamic circuitry underlies PPI (105).

Patients with schizophrenia (106) and SPD (107) show reproducible reductions in the magnitude of PPI, which is thought to lead to sensory overstimulation causing cognitive and behavioral confusion. Also, PPI deficits are induced in numerous experimental models of schizophrenia through, e.g., isolation rearing (108), ketamine (109), sleep deprivation (110, 111), and phencyclidine (112). The robust and reliable PPI reduction in schizophrenia can be restored, at least partially, with antipsychotic treatment, with some advantage of atypical compounds over first-generation, typical antipsychotics (113–119).

Importantly, reduced PPI has been observed in relation to elevated SPQ total, cognitive-perceptual and interpersonal scores (120), Minnesota Multiphasic Personality Inventory (MMPI) psychosis-proneness scores (121) and Eysenckian psychoticism scores (122). Evidence from a functional magnetic resonance imaging (fMRI) study of PPI points to reduced activation in the insula, putamen, thalamus, inferior parietal cortex, hippocampal gyrus, and fusiform gyrus in relation to higher levels of Eysenckian psychoticism scores (122). These BOLD patterns show some resemblance with the data obtained from samples of patients with schizophrenia (123). Of relevance to the present discussion, areas such as the putamen are rich in DA receptors, consistent with the hypothesis that PPI is at least in part dopaminergically mediated (124–126).

A final basic DA-mediated paradigm is latent inhibition (LI) (62, 127, 128). Comparable to PPI, LI is a cross-species phenomenon, which is sensitive to pro- and antidopaminergic challenges (62). LI refers to the finding that non-reinforced pre-exposure to a stimulus, that is later to be conditioned, causes less efficient conditioning when the same stimulus is subsequently reinforced. This phenomenon has been observed in both humans and animals. LI has also been investigated in relation to schizophrenia and schizotypy. A recent review showed reduced LI in the acute phase of patients with schizophrenia and preserved LI in chronic schizophrenia (129). That review also found a modest but relatively consistent relationship between schizotypy and LI, particularly of positive schizotypy (130). In particular, higher levels of positive schizotypy seem to be associated with less LI in healthy participants. These studies, together, suggest an involvement of dopaminergic alterations in the LI deficits in schizophrenia and positive schizotypy.

HIGHER COGNITIVE FUNCTIONS

Dopamine is thought to modulate the signal-to-noise ratio in semantic networks (131, 132). The reduction of prefrontal tonic dopaminergic modulation (hypofrontality) in schizophrenia is assumed to decrease the contrast between a signal and noise. This decreased contrast leads to a disinhibited spreading activation within semantic networks [see in Ref. (132) for an overview]. This increased spreading activation would result in remote associations (psychotic symptom) and enhanced semantic priming effects (laboratory measures) in schizophrenia (132). In healthy populations, on the other hand, an experimentally enhanced DA availability (levodopa consumption) focused such priming effects (133). Yet, this dopaminergic modulation of semantic networks differed for the two cerebral hemispheres with a hyperdopaminergia being more prominent in the right than left hemisphere (see previous section). This hyperdopaminergia (potentially resulting from a frontal hypodopaminergia) has been considered to explain the observation that enhanced spreading activation was more relevant for the right than left hemisphere in schizophrenia (134) and healthy individuals high in positive schizotypy (60, 135). Independent studies suggested that these DA-mediated functions explain both these lateralized priming effects and enhanced remote associative processing more generally (136, 137) as well as right-hemisphere shifts of functions in a broader sense. Indeed, the left hemisphere seems compromised in patients with schizophrenia with DA antagonists restoring if not reversing such altered hemispheric asymmetries (138–143).

Studies showed that lateralized lexical decision performance is relatively biased toward the right hemisphere in high as compared to low scorers on a positive but not negative schizotypy questionnaire (144, 145). In a pharmacological challenge study, superior left hemisphere language dominance was associated with elevated negative schizotypy scores in a levodopa (but not placebo) group (145). Thus, levodopa might restore left hemisphere language dominance in healthy individuals through (i) the attenuation of the contribution of the right hemisphere to language as a function of positive schizotypy and (ii) an increased contribution of the left hemisphere as a function of negative schizotypy. In an independent sample, but using the same task, the authors calculated signal detection theory measures of sensitivity (d-prime) and response tendency (criterion) (146). Results showed lower d-prime in the levodopa than in the placebo group in individuals low in positive schizotypy. For the response criterion, individuals in the placebo group showed a loosened versus conservative response criterion when being high versus low in positive schizotypy. In the levodopa group, these response tendencies were attenuated. This study suggests that a higher than normal DA availability (i) reduces d-prime in low positive schizotypy individuals and (ii) turns low positive schizotypy individuals less conservative and high positive schizotypy individuals more conservative in their response behavior.

Higher cognitive functions such as working memory and cognitive control have also been studied using experimental psychopharmacological designs. Using a between-subjects, double-blind, placebo-controlled design with groups of high and medium total SPQ scores, amisulpride, a clinically effective antipsychotic with strong D2/D3 receptor antagonistic action, improved working memory and verbal fluency performance in the schizotypy group but impaired it in the medium schizotypy control group (59). The same multi-center study investigated the effects of risperidone, a clinically effective atypical antipsychotic with action on D2 as well as 5-HT receptors, on performance on the antisaccade task, a prominent measure of response inhibition (147, 148). It was found that risperidone impaired antisaccade performance in the medium schizotypy group, whereas performance in the high schizotypy group showed a non-significant tendency toward improvement (149). These findings are in agreement with previous evidence of risperidone impairing antisaccade performance

in healthy controls (150) but improving it in patients with schizophrenia (151, 152).

To summarize, findings of this section suggest that individuals with high levels of schizotypy may benefit from DA agonists in terms of cognitive performance. In contrast, individuals with low levels of schizotypy may deteriorate in cognition with DA agonists. Concerning DA antagonists, people with high levels of (particularly positive) schizotypy may benefit in cognitive function from DA antagonistic compounds similar to patients with schizophrenia, or at least tolerate them. People with low or medium levels in (particularly positive) schizotypy may become impaired in these functions. Overall, given the role of DA in the effects of clinically effective antipsychotics (153), the presented data indicate that DA impacts some of the cognitive deficits observed in high (mainly positive) schizotypy (24, 78, 154). However, antipsychotics such as risperidone do not act only on the DA system, thereby limiting the implications for a dopaminergic basis of schizotypy (149).

SCHIZOTYPY AND DOPAMINE SYSTEM GENES

Twin studies have established that individual differences in the various subdimensions of schizotypy in the general population are to a significant part explained by additive genetic factors. Heritability estimates are in the range of 30–50% [see, e.g., Ref. (155–157)], although not all studies have found significant heritabilities (158). These behavioral genetic studies, thus, provide a basis for molecular genetic investigations such as those specifically targeting candidate genes related to the DA system.

The most frequently studied gene in the context of schizotypy is the gene coding for catechol-*O*-methyltransferase, the *COMT* gene (159–161). These studies were originally informed by significant associations of a single nucleotide polymorphism (SNP) in the *COMT* gene with schizophrenia (162); however, later meta-analyses have suggested that this association is not significant (163, 164). The COMT enzyme degrades catecholamines including DA in the synaptic cleft. Due to the paucity of the DA transporter in the prefrontal cortex, COMT plays a particularly prominent role in degrading pre-synaptic DA in that part of the brain. The *COMT* gene (located in chromosome 22q11.1-q11.2) contains a G to A missense mutation, resulting in a substitution of methionine (met) for valine (val) at codon 158 of the membrane-bound isoform of the protein (reference sequence identification code rs4680). This allelic variation (val158met) is a functional polymorphism: The met158 allele has about one third to one fourth of the activity of the val158 allele, resulting in less efficient catecholamine catabolism and, therefore, higher DA levels.

A number of published studies have reported associations between schizotypy and the *COMT* val158met polymorphism in healthy subjects. A series of publications from a large-scale study of apparently healthy young men, the ASPIS study, has provided evidence that the high-activity Val allele may be associated with schizotypy. In particular, the Val allele was found to be associated with elevated total SPQ and Perceptual Aberration Scale scores in a first analysis of 379 subjects (165). In a subsequent study using an extended sample of 543 individuals and a factor analysis of SPQ into four factors (cognitive-perceptual, negative, disorganization and paranoia) the Val loading was associated with increased total SPQ and increased negative and disorganized factor scores (71). In a further extension of 908 subjects where the analysis was also performed for individual SPQ dimensions, an association of Val with increased total SPQ, negative disorganized, and paranoia factors was observed. Additionally, there were specific relations of Val loading with increased scores in magical thinking, constricted affect, and odd speech subscales of the SPQ (166).

Broadly confirming this evidence, Grant et al. (167) observed in an independent sample of 280 healthy volunteers that Val/Val homozygotes had significantly higher positive schizotypy scores (O-LIFE unusual experiences) than Met carriers.

Other studies obtained evidence of an association between the Val allele and increased schizotypy in samples of relatives of psychiatric patients. One study (168) observed that among 81 first-degree relatives of schizophrenia patients the Val allele was associated with high negative schizotypy (social and physical anhedonia), while no association was found in 38 relatives of patients with bipolar disorder or in 30 healthy controls. Schürhoff et al. (70) studied *COMT* rs4680 and schizotypy in a combined sample of relatives of schizophrenic patients, relatives of bipolar patients and healthy controls (total $N = 106$). The authors observed higher total, positive and negative SPQ schizotypy (but not disorganization) scores in association with an increasing number of Val alleles.

Overall, these studies suggest that the Val allele is associated with higher levels of various schizotypy subdimensions. However, evidence to the contrary as well as failures to replicate have also been published. For example, Sheldrick and colleagues (169) reported higher SPQ-B Disorganization scores in the *COMT* Met/Met group than in the Val/Val group ($N = 522$ volunteers). Also, no significant association of overall schizotypy with rs4680 genotype was observed in individuals with velo-cardio-facial syndrome (170) or in a mixed sample of members from families with bipolar disorder as well as unaffected controls (total $N = 222$) (171). Ma and colleagues (172) similarly reported a lack of significant associations between rs4680 and SPQ total and subscale scores in 465 Chinese participants. Finally, Ettinger et al. (173) found no statistically significant association of positive schizotypy (RISC) with rs4680 in a small sample of healthy males ($N = 31$).

These inconsistencies remain to be resolved, both through additional original studies and a comprehensive meta-analysis that also addresses potential moderator variables. A number of factors may play a role, including the choice of schizotypy questionnaire (174) as well as the ethnic and sociodemographic composition of the sample (175). Other moderating variables may also be important. For example, the above mentioned study by Savitz and colleagues (171) observed, in the absence of an overall association of rs4680 with STA schizotypy, that there was an interaction between childhood trauma (as measured with the Childhood Trauma Questionnaire) and rs4680 on STA: The genotype was associated with STA only in individuals with higher trauma scores, such that Val/Val individuals showed increasing STA with increasing trauma, whereas other genotype groups did not. The possibility of interactive effects of genes and the environment is intriguing and needs to be examined in more detail.

In addition to *COMT*, a number of other DA-related genes have been investigated in relation to schizotypy. Ettinger et al. (173) obtained no evidence of significant associations of positive schizotypy (RISC) with polymorphisms in the *DRD3, DRD4,*

and *SLC6A3* genes in a sample of 31 healthy subjects. Grant et al. (167), however, reported significant associations of different O-LIFE subscales with *DRD2 Taq1A*, *MAOA*-uVNTR and *SLC6A3* in 288 participants. Finally, a recent study by Taurisano et al. (176) observed an association between SPQ total score and *DRD2* rs1076560 in 67 subjects, with GT heterozygotes showing higher scores than G allele homozygotes.

Overall, the discussed molecular genetic findings are promising but must be considered preliminary; they require replication and further investigation in larger samples. Genetic research has the possibility of informing the molecular basis of inter-individual variation in schizotypy and as such makes a unique, non-invasive contribution to the neuroscientific method arsenal available to schizotypy researchers. An additional appeal of this method is the possibility of combining genetic data with other neuroscience methods, such as functional and structural neuroimaging (177).

MOLECULAR IMAGING OF THE DOPAMINE SYSTEM IN RELATION TO SCHIZOTYPY

Measures of the DA system in humans can also be obtained *in vivo* using molecular imaging techniques such as PET and SPECT. These methods have been applied successfully to the study of the dopaminergic basis of schizophrenia (45). In contrast, relatively few PET or SPECT studies have investigated the relationship between DA system markers and schizotypy.

An early ^{123}I-IBZM single photon emission tomography investigation (178) reported a significant *negative* relationship between Eysenckian psychoticism scores and D2 receptor binding in the basal ganglia (relative to frontal cortex) in a small sample of healthy volunteers. Extending this first evidence, a [^{11}C]raclopride PET study (179) found lower D2 receptor density in putamen to be associated with higher scores on the Karolinska Scales of Personality detachment scale, a measure tapping aspects of negative schizotypy. Breier and colleagues replicated this finding, reporting a negative association between the Karolinska detachment scale and striatal D2 receptor binding using [^{11}C]raclopride PET in an independent sample of healthy volunteers (180).

In contrast, a more recent SPECT study observed a positive relationship between the disorganization score of the SPQ and D2/3 receptor binding in the right striatum (relative to occipital cortex) (181). Most recently, Taurisano et al. (176) used SPECT and found a positive correlation between D2 receptor binding in the right putamen and total SPQ score in individuals heterozygous for the *DRD2* rs1076560 genotype but not in individuals homozygous for the G allele, suggesting interactive effects of genotype and D2 availability on schizotypal personality. No association between whole striatum DA synthesis capacity and total SPQ score was observed in a PET study of subjects with persistent auditory verbal hallucinations (182).

A different line of molecular imaging studies has focused on dopaminergic challenges in relation to schizotypy. It has previously been shown that patients with schizophrenia, both in the acute phase and in remission, exhibit amphetamine-induced reductions in D2 and D3 DA receptor binding potential in the striatum (40, 183). This result suggests increased striatal DA release in schizophrenia and complements the evidence of heightened pre-synaptic DA function in this disorder (45). Interestingly, a similar pattern of increased striatal amphetamine-induced DA release has been observed in SPD (51). Further evidence confirming and extending this pattern across the schizophrenia spectrum comes from a [^{18}F]fallypride PET study (184). That study showed significant correlations between striatal DA release after a single administration of amphetamine and SPQ total and disorganized dimension scores in healthy volunteers (184). Together, these studies provide evidence for a common striatal dopaminergic dysregulation in both schizotypy and schizophrenia.

Finally, based on evidence of stress as a possible risk factor for schizophrenia (185), molecular imaging methods have been employed to investigate the effects of experimentally induced stress on DA turnover as a function of schizotypy. Using [^{11}C]raclopride PET, it was shown that participants with high levels of negative schizotypy – but not controls or participants with high levels of positive schizotypy – showed a significant stress-induced striatal reduction in binding potential (186).

Overall, studies using molecular imaging methods such as PET or SPECT are able to provide relatively direct markers of the DA system *in vivo* and, as such, can be used profitably to investigate its relationship not only to schizophrenia but also to schizotypy. However, evidence of associations between DA markers and levels of schizotypy in healthy participants is still scarce. To summarize, while there are associations between lower D2 receptor availability and higher psychoticism and detachment, there is also a report of an association between lower D2/3 receptor binding and lower disorganized dimension schizotypy. This pattern may imply differential associations of DA levels with different dimensions of schizotypy. Finally, there is evidence of increased striatal DA release following amphetamine administration or stress induction in schizotypy.

CONCLUSIONS

In this overview, we discussed studies linking DA and schizotypy. We first introduced the neurotransmitter DA and sketched some *in vivo* methods of its study in patients with schizophrenia and healthy controls. We presented evidence from the behavioral literature showing that high levels of schizotypy (in particular positive schizotypy) are associated with DA-sensitive functions, in line with behavioral tendencies previously reported in schizophrenia. In addition, we presented evidence that both increased (DA agonists) and decreased (DA antagonists) DA availability seems to be beneficial to behavioral deficits in high schizotypes (mainly positive schizotypy). Those low in schizotypy, however, seemed to deteriorate in their behavioral performance following antipsychotic treatment. While only a careful conjecture, it seems that an increase as well as a decrease of DA may restore function in high schizotypes but deteriorate it in low schizotypes. Overall, we conclude that variance in schizotypy may be explained in part by alterations to the DA system. Of course, as noted, the DA system does not act in isolation but in constant and complex interactions with other neurotransmitter systems.

An underdeveloped theoretical point not only here, but also in schizotypy research more generally, is a well-recognized framework integrating empirical evidence on links between DA and schizotypy from various levels of analysis (not only concerning DA) into a coherent theory. Important theoretical contributions

by Meehl (8, 9) and others (16, 187) have influenced our current thinking on schizotypy. A significant body of new data has been amassed that needs to be theoretically linked. In particular, we think of the psychopharmacological, imaging and genetic findings that are based on techniques that had not been available before. To achieve this aim, it may be instructive to turn in two directions for inspiration, viz. in the direction of (i) personality theory in individual differences research and (ii) clinical schizophrenia research.

Regarding individual differences, DeYoung (188) recently integrated previous assumptions into a theoretical framework that is relevant to our discussion of the role of DA in schizotypy. Particularly relevant is his discussion of "apophenia," i.e., individuals' tendency for overinclusive thinking and perception. Conrad (189) termed apophenia as the "unmotivated seeing of connections" accompanied by a "specific experience of an abnormal meaningfulness" (p. 46). For instance, one can refer to apophenia when individuals see and create pattern in random noise, whether this noise is perceptual (190, 191), semantic (136), or probabilistic (192). The suggestion of a link between apophenia and positive schizotypy in particular (136, 193) including its modulation by DA (60, 194) is not new. However, DeYoung (188) links apophenia not only with positive schizotypy and the positive symptoms of psychosis but adds another link, namely that apophenia can be predicted by openness, one of the personality traits of the five factor model of personality (195). Accordingly, apophenia can be called "openness to implausible patterns" [Ref. (188); p. 13]. This openness and its link to apophenia are hypothesized to stem from high-activity levels in the dopaminergic salience system. As mentioned above (44), recent theories on the role of DA in schizophrenia suggest that stressors dysregulate DA at the pre-synaptic control level. This is hypothesized to lead to changes in the appraisal of events, making them more salient (i.e., causing apophenia). Thus, DeYoung's (188) DA theory of personality is of interest as it ties schizotypy in with other personality traits and establishes parallels with schizophrenia at the cognitive (overinclusive pattern detection) and neurophysiological (DA) level.

These parallels link directly to the second direction of inspiration, i.e., clinical schizophrenia research. Here, aberrant salience has become a predominant topic. Current theorizing has provided promising explanations as to how DA links with the symptomatic expression of the clinical condition (153, 196). Specifically, these theories start to fill the explanatory gap between an apparent neurochemical disturbance in the brain and the formation of complex delusions and hallucinations. The argument is that delusions arise as a result of individuals' explanations of experienced aberrant salience. This argument is based on the role of DA in mediating both the presence or absence of reward and the salience, such as novelty, of stimuli. Increased DA neurotransmission is thought to lead to aberrant salience, that is, the direction of attention to objectively irrelevant internal or external stimuli. Delusions are by this account thought to arise through individuals' attempts to explain this distressing experience, likely in interaction with prior experiences and beliefs, both personal and socio-cultural. While it is not clear yet which aspect of salience is particularly disturbed in schizophrenia, this work provides a promising model for understanding an important symptom of schizophrenia. Additionally, it remains unclear from this work how other symptoms of schizophrenia, such as hallucinations, thought disorder and negative symptoms arise. Because we know of numerous established similarities between high schizotypy and schizophrenia [see in Ref. (24) for a recent overview], such theories may be drawn upon for our understanding of schizotypy as well.

In sum, we conclude that there is some evidence of an association between altered DA neurotransmission and schizotypy, particularly positive schizotypy. Such work informs not only neurobiological, but also cognitive models of the schizophrenia spectrum (196) and potential neuropharmacological treatments (197).

FUTURE WORK

The current overview illustrates the numerous and varied ways in which researchers have aimed to investigate the link between schizotypy and DA. The heterogeneity in the approaches and the sometimes conflicting results make it difficult to arrive at a clear-cut conclusion. Most of the time, we cannot directly compare results across study domains. This heterogeneity is of course frustrating but may also be constructive in providing directions as to where more work needs to be done.

Specific suggestions for future work include (1) the need to continue working on the development of an overarching theory of schizotypy (2), the assessment of the direction of effects of increasing and decreasing DA availability in high and low schizotypy of different dimensions (3), the role of concomitant illegal and legal drug use (4), the role of individuals' genetic makeup, and (5) the identification of schizotypal markers that are truly unfavorable concerning high-risk states and those that are potentially of little psychopathological impact.

In our view, the field needs both carefully controlled laboratory experiments and studies that account for the spontaneous self-administration of psychoactive ingredients that frequently act on the DA system. For instance, there is insufficient knowledge as to why schizotypal individuals and patients with schizophrenia consume DA-sensitive drugs to a higher degree than controls (198–200). It remains to be investigated whether this drug consumption is a potential trigger for psychosis or whether such individuals medicate themselves by altering their DA systems.

Also, inconsistencies in the literature remain regarding the molecular genetics of schizotypy. Future studies are needed to provide firmer answers on the important question of the molecular genetic makeup of schizotypy. Given the advance in sample sizes in the genetics of schizophrenia and the likely small sizes of genetic effects on schizophrenia spectrum phenotypes (201), it will be important to substantially increase sample sizes in the study of molecular genetic correlates of schizotypy. A promising way to achieve appropriate sample sizes is the establishment of multi-site collaborations under the guidance of consortia.

An additional avenue for future work concerns the direct comparison between individuals with high levels of schizotypy and patients with schizophrenia. While differences between individuals with high and low schizotypy scores have been shown on numerous occasions, much less is known about differences between highly schizotypal individuals and schizophrenia patients. Such a comparison would allow the identification of factors

that perhaps protect schizotypes from developing the full-blown clinical condition (24).

Finally, it should be pointed out as a limitation that this overview provides merely a qualitative discussion of the evidence of an association between DA and schizotypy. An important future contribution to this literature would be a formal meta-analysis of the size and significance of this association across different studies and methods.

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Psychotic-like experiences and their cognitive appraisal under short-term sensory deprivation

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Aims: This study aimed to establish and compare the effects of brief sensory deprivation on individuals differing in trait hallucination proneness.

Method: Eighteen participants selected for high hallucination proneness were compared against 18 participants rating low on this trait. The presence of psychotic-like experiences (PLEs), and participants' cognitive appraisals of these, was evaluated in three different settings: at baseline, in a "secluded office" environment, and in light-and-sound sensory deprivation.

Results: Psychotic-like experiences were experienced significantly more often in sensory deprivation for both groups. In particular, both experienced slight increases in perceptual distortions and anhedonia in seclusion, and these increased further during sensory deprivation. Highly hallucination prone individuals showed a significantly greater increase in perceptual distortions in sensory deprivation than did non-prone individuals suggesting a state-trait interaction. Their appraisals of these anomalous experiences were compared to both clinical and non-clinical individuals experiencing psychotic symptoms in everyday life.

Conclusion: Short-term sensory deprivation is a potentially useful paradigm to model psychotic experiences, as it is a non-pharmacological tool for temporarily inducing psychotic-like states and is entirely safe at short duration. Experiences occur more frequently, though not exclusively, in those at putative risk of a psychotic disorder. The appraisals of anomalous experiences arising are largely consistent with previous observations of non-clinical individuals though importantly lacked the general positivity of the latter.

Keywords: sensory deprivation, psychosis proneness, appraisals, anomalous body experiences, hallucinations

INTRODUCTION

Since around 2000 high risk research has increasingly investigated how psychotic-like experiences (PLEs) may be part of the risk trajectory for psychosis (1, 2). However, there is a long history of experimental paradigms attempting to induce such experiences in healthy individuals, much of it taking place back in the 1950s and 1960s. Many of these studies employed sensory deprivation of various kinds as the method for inducing anomalous experiences [e.g., Ref. (3)]. The findings were inconsistent, possibly due to an inadequate recognition of the complexity of the variables that enter into the situation of sensory restriction (4). Prolonged periods of deprivation were found to produce a range of psychotic-like phenomena in many, if not all participants. However, experiences at shorter durations varied depending on the nature of the deprivation, and the characteristics of the participants involved. Other studies (5, 6) concluded that PLEs occur in highly suggestible individuals who have a tendency to mistake "imaginary" events as veridical. Researchers lost interest in the field of inducing anomalous experiences, many dismissing the phenomena as more akin to fantasy or acts of imagination and not a true parallel of the hallucinations and other positive symptoms seen in psychosis.

While PLEs are interesting in their own right, we would propose that the theoretical construct of schizotypy conceived as a continuous dimension of risk is an important theoretical perspective from which to interpret individual differences in PLEs. Furthermore, the study of individuals with schizotypal characteristics has the advantage that results are not confounded by the contribution of variables such as hospitalization, medication effects, illness duration, and cognitive deficits. Within the theoretical framework of the continuum hypothesis, the study of a subclinical sample can lead the way toward understanding the perceptual–cognitive mechanisms underlying anomalous experiences both in and outside of psychosis.

With the potential utility for studying PLEs in the normal population now clearly re-established as part of the psychosis continuum (1) and schizotypy rubrics, researchers have taken a fresh look at methods to experimentally induce such experiences, with perhaps the most widely studied relating to the induction of auditory–verbal hallucinations. Many of these methods have been informed by recent theoretical accounts of "voice hearing" such as increased impact of top-down processing (7, 8), reality discrimination failure (9), and increased sensitivity to internally generated

percepts (10). Overall, several studies suggest a tendency to erroneously allocate an external source to internally generated stimuli may underlie hallucination proneness in schizophrenia [for review see Ref. (11)]. These findings support a tentative hypothesis that in sensory deprivation, where external events are absent or minimal, highly schizotypal, or hallucination prone individuals are more likely to erroneously process inner thoughts as being external events, and hence experience PLEs. A more sophisticated Bayesian framework (12, 13) suggests that psychotic symptoms arise from a disturbance in error-dependent updating of inferences and beliefs about the world. Corlett et al. (12), in particular, point out how several psychotomimetic drugs may come to have their effects by temporarily disturbing this cognitive process. They go on to discuss how sensory deprivation "may share phenomenological and biological similarities with the serotonergic hallucinogens, both occur when the top-down system imposes structure on noisy, unpredictable bottom-up signals" (p. 524).

In the modern era, several studies have attempted to use a sensory deprivation paradigm to induce PLEs in the normal population (14–18). Using more modern techniques, all studies were successful in inducing hallucinations of varying complexity in many of the participants. What is more, PLEs have been shown to be successfully induced using such methods with as little as 15 min exposure to deprivation of sight and sound (17). Mason and Brady (17) used an anechoic chamber (an environment of total light-and-sound deprivation) to induce PLEs (perceptual disturbances, paranoia, and anhedonia) particularly in those prone to hallucinatory experiences. This pilot study had a number of methodological limitations, not least its sample size of only 19 in total. The study was also criticized for the fact that the procedure included a "panic" button (19) on the basis that a previous study (20) showed the group with just such a button reported many more perceptual aberrations, and cognitive and emotional disturbances, including heightened anxiety. Bell (19) also suggested that the increased PLEs in the high hallucination prone group might be accounted for by differential anxiety levels between high and low-prone groups. This is a serious potential confound, it has been demonstrated that hallucination proneness is linked to trait anxiety (21), and in individuals with psychosis, acute anxiety is clearly linked to an increase in hallucinatory experiences (22). Therefore, it is feasible that an increase in anxiety brought about by sensory deprivation acts to mediate the relationship between PLEs and hallucination proneness. Anxiety was not measured in the original study and this omission was a major limitation. Assessment at baseline was also an area for technical improvement. The pilot study assessed this prior to entering the anechoic chamber when preparatory anxiety may have been influential. The current study utilized a further "secluded office" environment condition as a potentially better matched control condition than standard "baseline."

Cognitive models of psychotic symptoms (23) place central emphasis on how anomalous experiences are appraised. Among the range of appraisals, those that are externalizing and personalizing are thought to play a significant role in determining the transition to clinical psychosis and so are considered of particular significance. Garety et al. (23) also suggested that some people who have anomalous experiences may reject external attributions and so be protected in some way from developing full-blown psychotic symptoms such as delusions. Appraisals and the continuum of psychotic experiences have been studied in depth by Brett et al. (24). Their measure, the appraisals of anomalous experiences interview (AANEX), assesses anomalous experiences and individuals' responses to them, including their appraisals. Individuals with schizophrenia spectrum disorders appraised their experiences as more negative, more dangerous, more likely to be external and personally caused, and made more paranoid/conspiracy interpretations than non-diagnosed controls. Several subsequent studies (25, 26) have further elucidated, which AANEX appraisals distinguish clinical from "at risk" and healthy samples, and which predict greater distress. Assessment of appraisal of PLEs during sensory deprivation has not been described and is novel to this study.

AIMS AND HYPOTHESES

The current study aimed to replicate the effects of brief sensory deprivation using an anechoic chamber in larger groups of low and high hallucination prone individuals. A one-way microphone was also used to monitor participants rather than using a panic-button in an attempt to reduce potential demand characteristics. In addition, state and trait anxiety were measured as potential confounds/covariates. A further aim was to characterize the cognitive appraisals of PLEs arising in sensory deprivation using the AANEX and compare these to existing data.

It was hypothesized that:

1. The high schizotypy group would exhibit a greater degree of PLEs than the low group under normal baseline conditions. This helps further validate the measure of PLEs.
2. Both high and low hallucination prone groups would experience a significant increase in psychotic-like symptoms from baseline in sensory deprivation.
3. The increase in psychotic-like symptoms in sensory deprivation would be significantly greater for the high schizotypy group than the low schizotypy group.
4. The above effects would remain after controlling for any state/trait anxiety differences between the groups.

MATERIALS AND METHODS

PARTICIPANTS

Participants between the ages of 18 and 65 years were recruited via a university psychology department website that advertises to both students and the general public. Exclusion criteria included a history of a major psychiatric or neurological disorder, or recreational or psychotropic drug use in the past 3 months. An advert was placed inviting participants to complete an online version of the revised hallucinations scale [RHS: (27)]. Three hundred seventeen participants from a wide range of ethnic backgrounds returned data. From this sample, 76 low scorers and 39 high scorers were invited to participate as these conformed to the upper and lower 20th percentiles, according to questionnaire norms. Of these, 18 low scorers (7 males, 11 females, mean age = 25.39 years, SD = 6.09, mean score = 26.22, SD = 1.77) and 18 high scorers (4 males, 14 females, mean age = 24.94 years, SD = 3.95, mean score = 54.94, SD = 5.25) gave informed consent, consistent with university ethical procedures.

POWER ANALYSIS

Very little is known about the effects of sensory deprivation on people who rate highly for hallucination proneness, and so it was challenging to accurately estimate effect sizes from existing literature. The most similar study to date (17) reported large effect sizes for increases in perceptual distortions (partial $\eta^2 = 0.56$) and anhedonia (partial $\eta^2 = 0.58$) measured using the psychotomimetic states inventory (PSI) (28) immediately after 15 min of sensory deprivation. The power calculation for the current study was based on the smaller of these effect sizes – partial $\eta^2 = 0.56$. This is a conservative estimate for current purposes since participants in the current study spent a longer length of time in sensory deprivation (25 min) presumably providing greater opportunity for perceptual distortions to arise. Power calculations suggested that a minimum total sample of 18 per group would provide statistical power for a between-within participants repeated measures ANOVA design that exceeded 80% ($\beta = 0.80$), with $\alpha = 0.05$.

MEASURES

Revised hallucinations scale

This is a 24-item questionnaire based on the Launay–Slade hallucination scale (29) measuring a predisposition to experience hallucinations. It uses a revised scoring method, which allows participants to respond on a 4-point scale (1 = never to 4 = almost always). The scale has been shown to have good reliability and predictive validity, and moderately stable internal consistency over a period of 4–6 weeks (27).

Psychotomimetic states inventory

This is a 48-item questionnaire measuring psychosis-like experiences. Items are rated on a 4-point scale (from 0 = never to 3 = strongly), with some items being reverse scored (28). The PSI has sub-scales of delusory thinking, perceptual distortions, cognitive disorganization, anhedonia, mania, and paranoia. Originally developed for use in drug studies, it has produced meaningful results in a previous preliminary study of sensory deprivation (17).

State-trait anxiety inventory

A pair of two 20-item questionnaires that measure the temporary condition of state anxiety, and the more longstanding quality of trait anxiety. Items are rated of a 4-point scale. The state-trait anxiety inventory (STAI) has been shown to have good construct validity with multiple other assessment tools. It has also been shown to have good test-retest reliability [0.54 correlation for state, and 0.86 correlation for trait anxiety (30)].

Appraisals of anomalous experiences interview

A multidimensional measure of psychological responses to anomalies associated with psychosis (24). The first section (the AANEX inventory) includes items reflecting schneiderian first-rank symptoms and anomalies of perception, cognition, affect, and "individuation" (sense of distinction between self and others), as well as some "paranormal" experiences. The inventory generates two sets of scores: "lifetime" (not used in this study) and "state." For state scores, items are rated between 0 and 2 (absent, marginal, and present). The present study assessed whether a particular experience could be used to generate a state score.

The second section (the AANEX-CAR) is a structured interview that assesses appraisals, context, and responses pertaining to any anomalous experiences endorsed from the inventory. It can also be used independently from the inventory to explore anomalies elicited with other clinical instruments (in this instance, the PSI). The format is flexible, and different sub-sections can be used to assess current anomalous experiences, lifetime anomalous experiences, and also changes in interpretation and response style over time. Assessing a person's current style of appraising and responding takes approximately 10–15 min. The AANEX has been shown to reliably differentiate between clinical and non-clinical groups (24, 25).

PROCEDURE

Baseline data were collected from participants a few weeks prior to attending the testing facility (in order to minimize any anticipatory anxiety this may have caused on the day of the experiment itself). The baseline data-set for both groups included AANEX inventory state scores; STAI (full version); PSI. All participants submitted their data via an online website. In order to minimize order effects, participants in both groups were randomly split into two counterbalanced halves. The first half completed the deprivation condition first, followed by the seclusion condition separated by a half-hour break. These were reversed for the remainder. Following completion of the experiment, participants were debriefed, and received a nominal fee (the standard one set for psychology experiments) for their time in taking part.

DEPRIVATION CONDITION

The anechoic chamber and associated procedure is described previously (17). The amendments were the absence of a panic-button and presence of a microphone so that participants could be heard externally by the experimenter should they become distressed. Participants were informed that if they wished to terminate the experiment at any point they should remain seated and tell the experimenter, who would immediately restore light and communication. No participants chose to terminate the experiment early. After a period of 25 min within the chamber, participants were moved to an ante-room where they were immediately asked to complete questionnaires referring to the time that they had spent in the anechoic chamber: the AANEX inventory (state items only); STAI (state items only); PSI. For participants who reported clear anomalous experiences, the AANEX-CAR interview was also administered to gather data on appraisal and responding styles.

SECLUDED OFFICE CONDITION

Participants were seated in an unoccupied office for same period of time as the sensory deprivation condition. They then completed the same questionnaires/interview: AANEX inventory (state items only); STAI (state items only); PSI. Once again, if participants reported clear anomalous experiences, the AANEX-CAR interview was administered to gather data on appraisal and responding styles.

RESULTS

PRELIMINARY STATISTICAL ANALYSES

All statistical analyses were conducted using SPSS 17.0. Data were checked for normality before analysis using descriptive statistics

and histograms with normal distribution curves. Anxiety and PSI scores were normally distributed; however, AANEX scores violated parametric assumptions due to significant floor effects, and as a result were not submitted to analysis of variance. Since the AANEX and PSI were both used to measure the underlying construct of PLEs, a non-parametric test of correlation (Kendall's tau) was carried out to detect the strength of association between the two measures. There was a strong positive relationship between AANEX and PSI scores across all three conditions: baseline, $\tau = 0.54$, $p < 0.001$; seclusion, $\tau = 0.70$, $p < 0.001$; and deprivation, $\tau = 0.64$, $p < 0.001$. This supported the validity of using PSI scores as the measure of PLEs in the main analysis, despite this measure not having been formally validated for use in this experimental context. Age and sex were unrelated to PSI and anxiety scores and so were not considered further in analysis.

The order in which participants experienced seclusion and deprivation conditions was counterbalanced as part of the experimental procedure, however, a preliminary mixed between-within subjects repeated measures analysis of variance was carried out to test for any effect of order on anxiety or PSI scores. A significant main effect of order was found for both anxiety scores [$F(1,32) = 7.41$, $p < 0.01$] and PSI scores [$F(1,32) = 5.07$, $p < 0.05$], with participants who experienced seclusion first reporting higher anxiety and PSI scores throughout the experiment. There were no interactions between order and group, indicating that these order effects are not dependent on degree of hallucination proneness.

BASELINE GROUP COMPARISONS

It was hypothesized that the high scoring group would score significantly higher on measures of psychotic-like symptoms under normal baseline conditions. The high and low scoring groups did differ significantly in PSI scores at baseline [$F(1,34) = 6.145$, $p < 0.001$], with the high scoring group reporting a greater number of psychosis-like experiences (see **Table 1** for descriptives).

Baseline trait and state anxiety scores were significantly correlated ($r = 0.74$, $p < 0.001$). Significant differences in trait anxiety [$F(1,34) = 20.23$, $p < 0.001$] and state anxiety [$F(1,34) = 7.91$, $p < 0.01$] were found between the high and low hallucination prone groups at baseline, with the high hallucination prone group reporting higher levels of trait anxiety ($x = 47.78$, SD = 12.95 compared to 31.89, SD = 7.55) and state anxiety ($x = 42.28$, SD = 11.83 compared to 32.50, SE = 8.82). Although not specifically hypothesized all the above findings are in the expected direction.

PSYCHOSIS-LIKE EXPERIENCES ACROSS GROUPS AND CONDITIONS

It was hypothesized that while both groups would experience a significant increase in psychosis-like symptoms from baseline in near-total sensory deprivation, the increase would be significantly greater for the high scoring group. Results of a mixed between-within subjects repeated measures analysis of variance demonstrated a significant main effect of group for PSI scores [$F(1,34) = 31.31$, $p < 0.001$] (see **Table 1** for descriptives). This indicates that the high hallucination prone group experienced a significantly greater number of psychosis-like symptoms overall throughout the experiment, independent of condition (see **Figure 1**).

There was also a main effect of condition for PSI scores [$F(1,83) = 12.524$, $p < 0.001$] (see **Table 1** for descriptives). Planned contrasts revealed that PSI scores were significantly higher in deprivation than at baseline [$F(1,34) = 17.86$, $p < 0.001$] and PSI scores were significantly higher in deprivation than in seclusion [$F(1,34) = 14.05$, $p < 0.001$]. There was no significant difference in PSI scores between seclusion and baseline. There was no interaction effect detected between group and condition, suggesting that both high and low scoring groups responded in a similar way to the experimental conditions.

A further mixed between-within subjects repeated measures analysis of variance examining the PSI sub-scales of delusional thinking, perceptual distortion, cognitive disorganization, anhedonia, mania, and paranoia was conducted to investigate any difference in particular types of psychosis-like experiences reported across the different conditions. Consistent with hypotheses, there

Table 1 | Questionnaire mean scores for high and low hallucination-prone groups by condition.

Questionnaire scores	High scorers ($n = 18$)			Low scorers ($n = 18$)		
Revised hallucinations scale	54.94			26.22		
	Baseline	**Seclusion**	**Deprivation**	**Baseline**	**Seclusion**	**Deprivation**
Trait anxiety	47.78	–	–	31.89	–	–
State anxiety	42.78	36.33	38.89	32.50	33.17	36.17
AANEX	39.94	39.28	44.67	29.33	29.33	31.17
Psychotomimetic states inventory (sub-scales below)	37.00	36.83	49.28	13.83	19.89	27.11
Delusory thinking	4.83	4.94	5.50	2.17	1.78	2.22
Perceptual distortions	3.33	5.78	10.78	1.17	2.06	4.89
Cognitive disorganization	9.94	8.78	11.78	3.33	4.56	5.72
Anhedonia	9.17	8.06	10.56	3.67	6.83	8.72
Mania	5.89	6.17	7.28	2.78	3.89	4.50
Paranoia	3.83	3.11	3.39	0.72	0.78	1.06

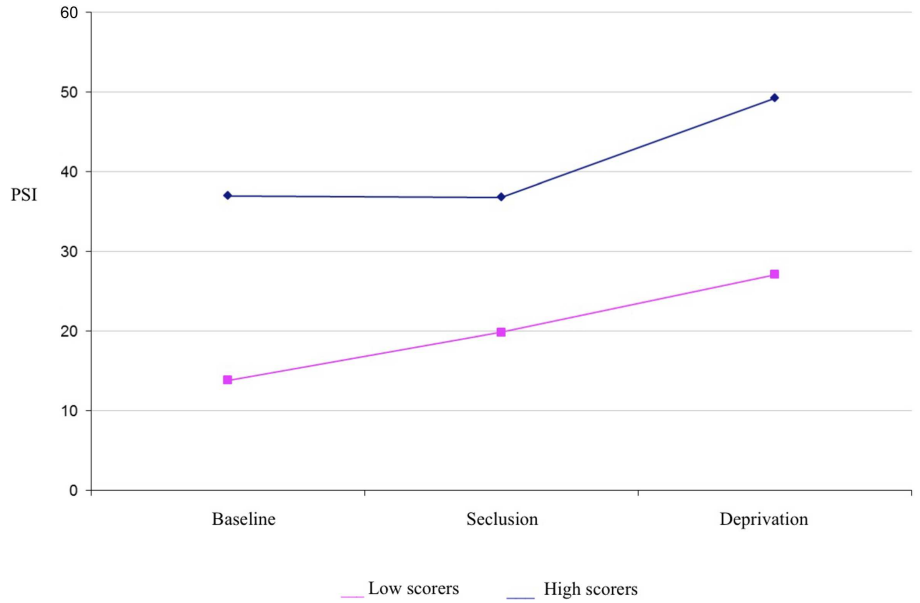

FIGURE 1 | Psychotomimetic states inventory scores in high and low hallucination-prone groups by condition.

was a significant main effect of condition for perceptual distortions [$F(2,68) = 34.15$, $p < 0.001$], anhedonia [$F(2,68) = 10.76$, $p < 0.001$], mania [$F(2,68) = 6.53$, $p < 0.01$], and cognitive disorganization [$F(2,68) = 3.22$, $p < 0.05$]. Planned contrasts indicated that perceptual distortions and anhedonia scores were significantly higher in seclusion than at baseline, and further increased during deprivation. Mania and cognitive disorganization were also significantly higher during deprivation than at baseline, but did not increase significantly in seclusion (see **Table 1**). A significant interaction between group and condition was found for the perceptual distortions subscale [$F(2,68) = 3.63$, $p < 0.05$], with high scorers showing a greater increase in these symptoms in deprivation than low scorers (a difference of around two SD, see **Table 1**). A significant interaction between group and condition was also found for the anhedonia subscale [$F(2,68) = 5.31$, $p < 0.01$], with low scorers showing a more marked increase in anhedonic symptoms in deprivation than high scorers (see **Table 1**).

STATE AND TRAIT ANXIETY ACROSS GROUPS AND CONDITIONS

Results of a mixed between-within subjects repeated measures analysis of variance demonstrated a significant main effect of group for state anxiety scores [$F(1,34) = 4.21$, $p < 0.05$] (see **Table 1** for descriptives). This indicates that the high hallucination prone group experienced higher state anxiety than the low hallucination prone group. There was no effect of condition for state anxiety, suggesting that anxiety did not differ between baseline, seclusion, and deprivation conditions (see **Figure 2**). Thus, state anxiety is unlikely to account for the differences in psychosis-like experiences between conditions. Trait anxiety differed between experimental groups, but did not correlate with PSI scores in any condition. Consequently, trait anxiety was not considered as a covariate for analysis of variance for PSI scores.

AANEX-CAR

AANEX-CAR semi-structured interviews were administered to all participants who reported clearly identifiable psychosis-like experiences in seclusion or deprivation. Interviews were indicated for 11 out of 18 participants in the high scoring group, and 4 out of 18 participants in the low scoring group. Consistent with PSI results, the hallucination prone group reported a greater number of psychosis-like experiences than the non-prone group ($\chi^2 = 4.11$, $p < 0.005$).

All interviews were indicated following experiences in deprivation. The types of experiences participants reported were varied, including hearing noises such as insects buzzing and whistling ($n = 2$); hearing music ($n = 2$); seeing shapes and colored lights ($n = 4$); visual hallucinations such as seeing faces and animals ($n = 2$); out-of-body experiences or the experience of watching events through another's eyes ($n = 3$); disorientation such as feelings of falling, the room spinning, and the walls closing in ($n = 2$). Interviews were scored according to the procedure described by Brett et al. (24), and ratings derived for appraisal dimensions, appraisal categories, emotional response, cognitive and behavioral response, perceived social understanding, and perceived controllability.

In order to establish whether AANEX-CAR scores reflected typical appraisal and cognitive/emotional response styles of people experiencing genuine symptoms that had not been experimentally "induced," the scores were compared with existing data from a clinical group (schizophrenia spectrum disorders) and a non-clinical group with anomalous experiences [Ref. (25), see **Table 2**]. Experiences under sensory deprivation were similar to those seen in the non-clinical group and differed from the clinical group in being appraised as less dangerous, less external, less due to others, and less anxiety provoking/negative emotionally; and as having a greater sense of agency, and more likely to have a psychological

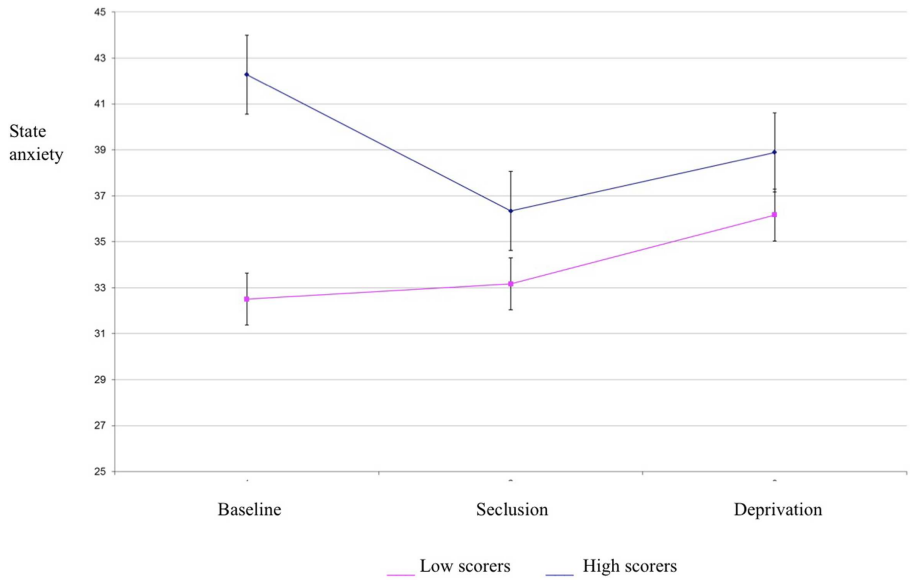

FIGURE 2 | State anxiety scores in high and low hallucination-prone groups by condition.

cause. However, the sensory deprivation group's appraisals differed from the non-clinical group in not being as positively valenced; not as spiritual in meaning; or positive emotionally. In these latter respects they did not differ significantly from the clinical group.

DISCUSSION

Consistent with hypotheses, hallucination proneness was associated with greater psychosis-like symptoms under all conditions. In addition, both high and low scoring groups experienced a significant increase in psychosis-like symptoms in sensory deprivation conditions. Sensory deprivation was found to produce a significant increase on four sub-scales of the PSI: perceptual distortions, anhedonia, mania, and cognitive disorganization. Findings with respect to perceptual distortions and anhedonia were highly marked and were consistent with the pilot study (17). However, unlike the previous study, paranoia did not appear to increase significantly. As the current study is larger and so better powered, and utilized a longer time period, it is likely to provide a more sensitive profile of the psychotic-like symptoms provoked by deprivation. In the current study, an interaction effect between condition and group was only seen for the perceptual distortion subscale clearly validating the RHS and suggesting a state-trait interaction. Consistent with this, the majority of hallucination prone individuals (11 of 19) reported clear anomalous experiences sufficient for AANEX-CAR interview, in contrast with a minority of non-prone (4 of 19). The potential role of state and trait anxiety was explored. Consistent with the previous literature (21), trait and state anxiety distinguished the high hallucination-prone from the low hallucination-prone groups at baseline. However, trait anxiety neither predicted changes in PSI scores nor differed across condition in either group. Therefore, the increase in psychosis-like symptoms seen in both groups during deprivation cannot be readily attributed to increased anxiety.

The considerable presence of anomalous perceptions that were experienced to some degree at least as autonomous, external, and "hallucination-like" are consistent with the "faulty source monitoring" hypothesis (9). It is also consistent with the framework offered by Fletcher and Frith (13) that unusual perceptions arise out of an abnormality in the brains' inferencing mechanism, so that new evidence (including sensations) is not properly integrated, leading to false prediction errors in psychotic and psychosis-prone individuals. In the absence of external stimuli, perceptual distortions are presumably internally generated by the individuals, but are misattributed as external in origin due to "top-down" processes (12). Overall, the range and frequency of psychotic-like symptoms are sufficient to endorse Corlett et al.'s (12) position that sensory deprivation offers a promising model of psychosis in psychiatrically healthy individuals. Future research should explore the underlying neurocognitive mechanisms of PLEs under sensory deprivation using neurobiological methods such as psychophysiological recording.

Also of interest, but not predicted, was that *low* scorers experienced a significantly greater increase in anhedonic symptoms during deprivation as compared to baseline measurement. Previously, this finding had only been seen in high scorers. This could be due to boredom effects in the low scoring group (related to the longer time duration), who otherwise reported few psychosis-like experiences during deprivation.

AANEX-CAR data showed the appraisal and cognitive/emotional response styles of participants were broadly consistent with those of non-clinical individuals with anomalous experiences. Participants strongly believed that the causes of their experiences were psychological in nature and that they had some agency within them. The unusual environmental context may have made them more likely to interpret their experiences in terms of internal mental processes. Anxiety, dangerousness, and

Table 2 | Appraisals under sensory deprivation compared with Lovatt et al. groups (25).

AANEX-CAR items	Sensory deprivation group ($n = 15$) mean (SD)	Clinical group ($n = 29$) mean (SD)	Non-clinical group ($n = 29$) mean (SD)	*F* test	*Post hoc* comparisons (Scheffe)
APPRAISAL: DIMENSIONS					
Valence	2.93 (1.24)	2.52 (1.25)	4.19 (1.04)	14.23**	NC > C = SD
Dangerousness	2.66 (1.74)	3.81 (1.18)	2.74 (1.10)	5.85**	C > NC = SD
Externality	2.00 (1.10)	3.44 (1.25)	2.33 (0.92)	10.61**	C > NC = SD
Agency	4.47 (0.72)	3.85 (1.2)	2.44 (1.15)	19.46**	C > NC = SD
APPRAISAL: CATEGORIES					
Biological	0.07 (0.25)	0.48 (0.80)	0.44 (0.80)	n.s	–
Psychological/normalizing	2.00 (0.00)	0.44 (0.75)	1.44 (0.75)	29.90**	C > NC = SD
Spiritual	0.33 (0.70)	0.67 (0.78)	1.33 (0.88)	8.54**	NC > C = SD
Other people	0.07 (0.25)	1.11 (0.93)	0.74 (0.26)	23.03**	C > NC = SD
EMOTIONAL RESPONSE					
Neutral arousal	2.33 (1.19)	2.59 (1.25)	2.70 (1.07)	n.s	–
Negative emotional response	2.12 (1.54)	3.70 (1.07)	2.00 (0.92)	17.09**	C > NC = SD
Positive emotional response	2.07 (1.24)	2.19 (0.92)	3.15 (1.13)	7.05**	NC > C = SD
Self-rated anxiety	2.53 (1.31)	3.96 (1.02)	1.96 (1.06)	22.69**	C > NC = SD
Self-rated excitement	2.27 (1.34)	2.48 (1.48)	3.03 (1.45)	n.s.	–

NC, non-clinical group; C, clinical group; SD, sensory deprivation group.
***$p < 0.01$.*

a negative emotional response were at the low levels seen in non-clinical individuals, and unlike the symptomatic experiences of those with psychotic disorders. However, non-clinical individuals with repeated anomalous experiences have often been shown to develop positively valenced appraisals with, for some, strong spiritual meanings. This did not prove the case, in general, for those in sensory deprivation. "Naturally" occurring – and reoccurring – anomalous experiences are plausibly more likely to develop idiosyncratic and personally highly meaningful appraisals than those "artificially" created by laboratory conditions.

LIMITATIONS

Despite attempting to address several potential confounds of the pilot study, other such as social desirability are suggestibility cannot be excluded and deserve further testing. Though the appraisal data go some way to detailing the similarities with clinical and non-clinical psychotic experiences there is some way to go before concluding the phenomena seen in sensory deprivation are equivalent as this is currently reliant on self-report. Biometric approaches such as psychophysiological or neurocognitive indices would clearly strengthen the argument.

The "secluded office" condition attempted to provide a closer analog to sensory deprivation (in duration at least) than the baseline but this was not highly successful. While, on many indices these two conditions appeared highly similar there were significant order effects across both groups, with participants who experienced seclusion first reporting more psychosis-like experiences throughout the experiment. It is possible that participants who experienced seclusion first responded to the perceived demand characteristics of the experiment, endorsing more items on the PSI and AANEX measures in this first condition. Counter-balancing was incorporated into the experimental design in an attempt to moderate any order effects, but demand characteristics may still have had some impact particularly on the seclusion data. As a consequence, the baseline condition is very probably the more stable one against which to compare the experimental deprivation condition.

CLINICAL IMPLICATIONS

The findings suggest that even during a quite brief period of sensory deprivation, perceptual distortions, and other psychosis-like experiences are common in the "normal" population. Although high hallucination prone individuals reported significantly greater levels of perceptual distortions, individuals not prone to experiencing hallucinations were also affected. In the current study, any psychosis-like symptoms were transient, and quickly resolved once participants were returned to normal conditions. Indeed, the distortions and other psychotic phenomena induced did not bring attendant anxiety as probably occurs with many early psychotic symptoms. Nevertheless, it is possible that a longer period of deprivation may have the potential to induce enduring symptoms of psychosis with consequent distress.

CONCLUSION

Overall, the study provides further support for use of sensory deprivation as a non-pharmacological tool for temporarily inducing psychotic-like states. Both high and low hallucination prone groups responded to sensory deprivation in a qualitatively similar manner, but with quantitative differences in the frequency of psychosis-like experiences reported. It appears possible to accurately predict individuals who are most likely to experience psychosis-like experiences in sensory deprivation based on the presence/absence of schizotypal traits (here as indexed by hallucination proneness). Sensory deprivation would seem a useful paradigm to model psychotic symptoms, to which we would add the important ethical principle of non-harm.

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Factor analysis demonstrates a common schizoidal phenotype within autistic and schizotypal tendency: implications for neuroscientific studies

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Behavioral and cognitive dysfunction, particularly social and communication impairments, are shared between autism and schizophrenia spectrum disorders, while evidence for a diametric autism-positive schizophrenia symptom profile is inconsistent. We investigated the shared phenotype at a personality trait level, particularly its resemblance to schizoid personality disorder, as well as differential aspects of the autism–schizophrenia model. Items of the autism spectrum quotient (AQ) and schizotypal personality questionnaire (SPQ) were pseudo-randomly combined, and were completed by 449 (162 male, 287 female) non-clinical participants aged 18–40. A factor analysis revealed three factors; the first represented a shared social disorganization phenotype, the second reflected perceptual oddities specific to schizotypy while the third reflected social rigidity specific to autism. The AQ and SPQ were strongly correlated with Factor 1 (AQ: $r = 0.75$, $p < 0.001$; SPQ: $r = 0.96$, $p < 0.001$), SPQ score was correlated with Factor 2 ($r = 0.51$, $p < 0.001$), particularly in cognitive–perceptual features ($r = 0.66$, $p < 0.001$), and AQ score was strongly correlated with Factor 3 ($r = 0.76$, $p < 0.001$). Furthermore, there was no relationship between Factor 1 and Factor 2. Thus, there is robust evidence for a shared social disorganization phenotype in autistic and schizotypal tendency, which reflects the schizoid phenotype. Discriminating and independent dimensions of schizotypal and autistic tendency exist in Factors 2 and 3, respectively. Current diagnostic protocols could result in different diagnoses depending on the instrument used, suggesting the need for neuromarkers that objectively differentiate autistic and schizotypal traits and resolve the question of commonality versus co-morbidity.

Keywords: autistic traits, schizotypal personality traits, schizoid personality disorder, factors analysis, autism, schizophrenia

INTRODUCTION

The phenotypic tangle of autism and schizophrenia spectrum symptomology has been hotly debated since Bleuler defined "autism" in 1911 as an exclusive psychiatric disorder (1, 2). Despite their obvious clinical differences in symptom onset and presentation, interpersonal and cognitive deficits, and disorganization are fundamental to both disorders (1, 3–9), yielding a potential confusion in diagnosis.

Autism and schizophrenia (the terms "autism" and "schizophrenia" refer to the full spectra of the respective disorders) are neurodevelopmental disorders with pervasive social impairments such as flattened facial and speech affect, reduced gesturing, eye contact and language, concrete and obsessional thinking, and unusual body movement (10). King and Lord (11) pointed to symptom similarity between schizotypal personality and autism in terms of unusual preoccupations, unusual perceptual experiences, odd thinking and speech, constricted affect, social anxiety, lack of close friends, and odd or eccentric speech and behavior. A clinical diagnosis of autism spectrum disorder (ASD) specifies early childhood presentation of social and communication dysfunction, in conjunction with restricted and repetitive behaviors (10). Schizophrenia is typically qualified with the onset of a psychotic episode, marked by hallucinations, delusions, disorganization, and/or catatonic behavior for up to 1 month, in late adolescence or early adulthood. Schizophrenia diagnoses can be established only if the psychosis is accompanied by enduring affective and interpersonal dysfunction, and disorganization in speech and behaviors (10).

The newly released Diagnostic and Statistical Manual of Psychiatric Disorders version five (DSM-5) (10) is naturally controversial due to its central role in clinical diagnosis, and the revision of symptom discrimination, differentiation, and co-morbidity. The new edition saw the removal of paranoid and schizoid personality disorder (PD), which may be detrimental to diagnostic specificity. Schizoid PD, as defined in DSM-IV-TR (12), describes pervasive social dysfunction and negative symptoms that are central to schizophrenia (including schizotypal PD). Such symptoms are also seen in autism. Core features of schizoid PD include: lack of interest in, and active avoidance of social situations both in occupation and daily life, restricted affect, odd communication, relationship detachment, and poor empathy. Mental rigidity and single-minded pursuit of interests are also characteristic (12–14).

These features can indirectly lead to positive-like symptoms such as fantasies, mania (13), and paranoid ideation (11). Schizoid PD, thought to be a milder form of schizotypal PD, has the potential to progress into more enduring schizophrenia spectrum disorders, with a genetic association to schizophrenia (14, 15). In fact, in a study of 32 children diagnosed with schizoid PD, 24 met the criteria for schizotypal PD, and two developed schizophrenia (14). Exclusion of schizoid PD was based on a lack of empirical evidence for the disorder. Schizoid PD was reported to have only 1% pathological prevalence (13), compared to 3% prevalence of schizotypal PD (12).

DSM-5, in similar vein, aligns Asperger's disorder with ASD resulting in the abolishment of key differential diagnostic criteria. Removing language delay and early onset symptom presentation criteria for ASD consequently reduces the discriminatory quality of diagnosis. Wolff et al. (14) suggest distinguishing between schizotypal PD, schizoid PD, and Asperger's disorder is not warranted. Thus, the relaxed exclusion criterion for ASD, and removal of schizoid PD, impacts the diagnosis, prognosis, and therapeutic techniques for autism and schizophrenia spectrum disorders. More accurate assessment of the schizoid phenotype may indeed reduce confusion between the apparent comorbid social dysfunction in the autism and schizophrenia spectra (13).

Social–cognitive dysfunction is evident in both autism (7, 16–19) and schizophrenia (7, 16–22). Social cognition is defined as the cognitive aspects of the social experience; including perceptions, processing, and interpreting social information (23) from basic facial affect recognition to theory of mind (22). Social anhedonia – social isolation and disinterest, is a prodromal, as well as an active and residual feature of schizophrenia (24, 25). Social anhedonia has also been found to predict severity in autism (26). However, it has been argued that social deficits in autism represent social anxiety and social skills, while negative schizotypy relates to social anhedonia and depression (27). The similarity between the two disorders in terms of social cognition and interpersonal deficit may lead to confusion in symptom interpretation, and consequently result in misdiagnosis (9, 22).

Due to the spectrum nature of both disorders, symptoms in the general population grade from clinical pathology to personality traits (1). Self-report measures such as the autism spectrum quotient (AQ) (28) and Schizotypal Personality Questionnaire (SPQ) (29) reliably identify autistic and schizotypal traits, respectively among clinical (3, 4, 6, 30–32) and non-clinical populations (5, 33–35). The AQ contains five subscales that reflect the DSM-IV criteria for autism: social skills, attention to detail, attention switching, communication, and imagination (36). The SPQ provides a measure of schizotypal tendency in accordance with the nine DSM-III-R criteria for schizotypal PD (37). Three superordinate dimensions encapsulate these nine subscales: Ideas of reference, odd beliefs, unusual perceptual experiences, and suspiciousness (cognitive–perceptual/positive); excessive social anxiety, no close friends and constricted affect (interpersonal/negative); odd behavior and odd speech (disorganized) (29, 38). A brief version of the SPQ (SPQ-B) was introduced in 1995 by Raine and Benishay (39) and then revised in 2010 by Cohen et al. (SPQ-BR) (40). Cohen et al. (40) reduced the SPQ to 32-items within seven subscales, uniting Ideas of Reference and Suspiciousness, and No Close Friends and Constricted Affect (40). Despite the obvious benefits of creating a briefer scale, the full-scale SPQ provides a comprehensive measure of schizotypy based on schizotypal PD, unlike the brief versions revised based on non-clinical student samples. Furthermore, in reducing the number of response opportunities, valuable information about the diversity of the schizotypal phenotype may well be missed. The SPQ-BR has only three or four items representing each of the nine criteria for schizotypal PD (40), compared with the seven to nine questions representing the same criteria in the full-scale SPQ (29). This relative paucity of assessment may result in noisier data, likely affecting diagnostic predictive power.

Autistic traits are particularly similar to disorganized (3–6) and interpersonal features of the SPQ (3, 5, 33, 34). Furthermore, Schizotypal tendency, quantified by the SPQ, is significantly higher in autism (3, 6) and Asperger's disorder (4, 5) than in controls, while AQ-measured autistic tendency is higher in schizophrenia (3, 31, 32). The common social–interpersonal dysfunction and communication–disorganization in schizotypal PD and Asperger's disorder may reflect true comorbid symptoms. Alternatively, the apparent co-morbidity could result from a lack of differentiation between distinct symptoms by measurement tools (5).

The diametric model argues that positive or cognitive–perceptual features are opposed to the social aspects of autism (3, 5, 33–35). The AQ's imagination subscale quantifies a rigidity of thought and convergent thinking, which is in contrast with the fluidity of thought characterizing schizophrenia (5, 41). Crespi and Badcock (2) suggested that social–cognitive dysfunction in autism is diametric to that in schizophrenia. Specifically, that social–cognitive dysfunction is under-developed in autism and over-developed in schizotypy (leading to hyper-developed theory of mind). Nevertheless, positive schizotypal features remain stronger in autism than controls (6, 35), and paranoid thinking in autism and schizophrenia may be a subsequent consequence of social–communication misperceptions (11). Furthermore, SPQ unusual perceptual experiences and Odd behavior's mimic AQ predictors of abnormal sensory responses and restrictive/repetitive behaviors, respectively (4). Altogether, the core social dysfunction, with evidence of broad trait similarities provides support for a shared schizoid phenotype in autism and schizophrenia spectrum disorders.

Dinsdale et al. (35) supported a shared social and communication dysfunction in autistic and schizotypal tendency, as well as supporting the diametric model of positive schizotypy and autism. The authors ran a principal component analysis (PCA) of combined AQ and SPQ-BR subscales revealing two components. The first component reflected social–communication disinterest, impairment, and abnormalities with predominant contributions from the AQ subscales social skills and communication, and SPQ-BR subscales constricted affect, social anxiety, odd behavior, and ideas of reference. The second component reflected a pattern of diametric social autism and positive schizotypy. Substantial contributions from SPQ-BR subscales Odd beliefs and unusual perceptions loaded positively and AQ subscales of social skills and imagination loaded negatively create an autism-positive schizotypy axis (35). The authors also carried out their own PCA analysis of Wakabayashi et al.'s (34) full-scale SPQ and AQ data (35).

The resulting two-component solution supported their own PCA results, however, differences in subscale contribution to the components suggests that the full-scale SPQ provides a more robust division of subscales than does the brief form. Specifically, attention switching was exclusive to the first component, odd behavior contributed equally to both components, and ideas of reference contributed more substantially to the second component (35). Put simply, in Wakabayashi et al.'s dataset, the first component appears to better represent a social behavioral dysfunction, while the second gives a stronger representation of cognitive–perceptual and disorganized subscales. Overall, the first component from both datasets supports a co-morbidity of traits within the broader social dysfunction phenotype in autistic and schizotypal tendencies, particularly those specific to Asperger's disorder and schizoid PD (35).

It is noteworthy that in these studies, the questionnaires were presented individually on different response scales (AQ: 4-point scale, SPQ-BR: 5-point scale, SPQ: 2-point scale), affecting response specificity and statistical analysis. Furthermore, the total contribution of the components to the total variance in their data was quite low in both datasets, at around 45%. PCA may not be the ideal analysis for this type of data, as it aims to simply reduce a large dataset to a smaller set of components exploring patterns in the data (42). All of the variables variance is included in the PCA, limiting the capacity to identify meaningful underlying constructs, thus, rendering it uninterpretable (43, 44). Factor analysis, on the other hand, can more accurately reveal the underlying constructs as only the variance that is shared among the variables is analyzed (42, 45). Factor analysis is recommended when there is a theoretical basis for a conceptual relationship between the variables (43), thus, this study will adopt factor analysis as the preferred method, and PCA simply to compare with Dinsdale et al. (35).

Co-morbidity between the disorders is seen at a clinical level. Solomon et al. (7) found that 20% of their high risk and first episode schizophrenia participants also met the criteria for autism. Waris et al. (8) identified pervasive developmental disorder (PDD – the diagnostic category in which ASD lies) in 10 of 18 adolescents with schizophrenia, and Rapoport et al. (46) found 20–30% of children with schizophrenia had prodromal and comorbid PDD, and expressive and receptive language deficits. Also, stress-induced behavior in autism can be additionally or misdiagnosed as schizophrenia (47, 48). These studies give evidence of the risk of incorrect behavioral assessment in autism and schizophrenia. Children with Asperger's were indistinguishable from "loner" (parent rated schizoid personality traits) children on a schizoid scale (49) suggesting potential misclassification of schizoid PD as Asperger's disorder due to comorbid schizoid trait in "loner" and Asperger's children. Schizoid PD, until its removal, was differentiated from schizotypal PD in its lacking positive symptom, identical to the distinction of autism from schizotypal PD (12). Misdiagnosis must be avoided in order to eliminate wrongly prescribed psychopharmacological medications, which may have limited success, instead exposing patients to potentially harmful side effects.

The argument for a shared phenotype is further reinforced by genetic and neuroimaging studies, providing an objective link between the disorders. Genome-wide association studies have found genetic overlap in copy number variants between schizophrenia and autism, suggesting similar processes in the development and regulation of synaptic transmission that influence common biological pathways in the two disorders (50). The heritability within and between autism (2, 50, 51) and schizophrenia (2, 10, 12, 50, 52) evidences a common biological foundation between the disorders (46, 50, 53, 54). Furthermore, schizoid traits are more likely in parents of children with autism (55), and parents of children with autism more likely to have a history of a mental disorder, particularly schizophrenia, than control parents (56). Similar social–cognitive neural dysfunction in conjunction with genetic associations further supports the schizoid phenotype as a link between autism and schizophrenia. Altogether, these studies underline adverse implications in the subjective nature of the DSM clinical classification process (50, 57).

Neuroimaging studies directly comparing autism and schizophrenia identify a neural network related to social cognition (18, 58) and other functional and structural similarities (19, 22, 58–62). Gray matter reduction around the STS and limbic-striato-thalamic network is associated with the degree of autistic tendency in schizophrenia and autism (31, 59, 61, 62). Metabolite similarities, such as glutamate, glutamine, gamma-aminobutyric acid (GABA), and *N*-acetylaspartylglutamic acid (NAAG) are related to negative symptoms of schizophrenia (63, 64) and autism (65), and have also been associated with social–cognitive dysfunction in both disorders [see Rossignol for a review (65, 66)]. On the other hand, reduced *N*-acetylaspartyl acid (NAA) has been associated with more severe symptoms in schizophrenia, particularly positive symptoms (64, 67) and reduced social functioning, but not negative symptoms alone (67). Reductions in NAA have also been identified in autism (65, 68), suggesting a common neurotransmitter link between the spectrum disorders and opposing the argument for diametric disorders.

To our knowledge, no previous study has explored the factor structure of a combined, pseudo-randomized version of the original SPQ and AQ (ASQ). Items were presented on a four-point Likert to reduce response bias and yield more reliable participant reports (69). The aim of this study was to extend Dinsdale et al.'s findings via a PCA of the complete ASQ followed by factor analysis in order to identify the underlying constructs (43–45). Furthermore, the study aimed to uncover a more robust phenotypic model for autism and schizophrenia spectrum disorders at a trait level, with particular interest in the schizoid phenotype. It was expected that, as with Dinsdale et al. (35), the ASQ PCA would reveal a factor specific to social AQ (social skills, communication, and attention switching) and Interpersonal SPQ (no close friends, constricted affect, and social anxiety), reflecting schizoid PD. In using only the shared variance in the model, and allowing the resulting factors to correlate, this research explored how cognitive–perceptual subscales (ideas of reference, odd beliefs, unusual perceptual experiences, and suspiciousness) contributed to the model. It was expected that the disorganization subscales would contribute across factors, as these traits are related to both social AQ and interpersonal and cognitive–perceptual dysfunction. In terms of the factor analysis, we expected that a similar model structure would emerge, but that this would provide a more robust model of the underling constructs within autistic and schizotypal traits. Furthermore, we predicted a strong relationship

between the interpersonal dimension of the SPQ and AQ social subscales: social skills, attention switching, and communication.

MATERIALS AND METHODS

PARTICIPANTS

Participants were sourced through social media and advertisements targeting the general population. A total of 449 adults aged between 18 and 40 years, 162 males (mean = 24.20, SD = 4.92) and 287 female (mean = 23.08, SD = 5.01), volunteered for the study, accessing and completing a combined questionnaire online. On average males were older than females [one-way ANOVA, $F(1,448) = 5.22$, $p < 0.05$]. The Swinburne University Human Research Ethics Committee approved the collection of participant data; informed consent was obtained from each participant prior to completing the questionnaire.

MATERIALS

Autistic tendency was measured with Baron-Cohen et al.'s (28) AQ comprising 50 items within five subscales: social skills, attention switching, attention to detail, communication, and imagination. Schizotypal tendency was quantified using Raine's (29) 74-item SPQ. The SPQ has nine subscales in accordance with the DSM III-R diagnostic criteria of schizotypal PD, which represent the three core criteria of schizophrenia: cognitive–perceptual (ideas of reference, odd beliefs, unusual perceptual experiences, and suspiciousness), interpersonal (social anxiety, no close friends, and constricted affect), and disorganized (odd behavior and odd speech) (12, 29, 36, 38). Including the full-scale SPQ provided a richer schizotypal trait dataset, while also allowing the extraction of the 32-items that create the SPQ-BR. Subsequently, comparisons against both Dinsdale et al.'s and Wakabayashi et al.'s findings were made (35). Furthermore, we were able to identify any potential confounds of the SPQ-BR, as highlighted previously in relation to the PCA of Wakabayashi et al.'s data (34) conducted by Dinsdale et al. (35).

The original dichotomous "yes/no" response format of the SPQ raises concerns over trait insensitivity and social desirability response bias (70). A Likert scale design has been shown to improve internal reliability and convergence of the SPQ (70) and consequently this study employed a 4-point Likert scale to align with the AQ. Thus, creating a cohesive set of items that was not particularly associated with either questionnaire. The AQ and SPQ items were then combined, pseudo-randomized, and presented online with Opinio (71). Participant responses to combined AQ and SPQ (ASQ) items ranged from 1: "strongly agree," to 4: "strongly disagree." In broadening the response options from yes/no (2-point), and removing the "neutral" option in the 5-point scale, the opportunity for respondents to make a conservative response to potentially socially undesirable questions is reduced. There was acceptable internal consistency for SPQ total ($\alpha = 0.86$) and its superordinate subscales (cognitive–perceptual $\alpha = 0.77$; interpersonal $\alpha = 0.77$; disorganized $\alpha = 0.69$), AQ total ($\alpha = 0.66$), and ASQ total ($\alpha = 0.88$).

PROCEDURE

Participants volunteered to complete the online ASQ through the Opinio website (71). Raw ASQ item scores were converted to zero (0) for an unendorsed response ("strongly disagree" or "disagree") and one (1) for an endorsed response ("strongly agree" or "agree"). AQ and SPQ items were then extracted from the combined questionnaire to obtain conventional AQ (/50) and SPQ (/74) scores. Participants' individual subscale and total scores were entered into SPSS Version 20.0 for statistical analysis (72).

DATA ANALYSIS

An initial one-way analysis of variance (ANOVA) for gender differences in total AQ and SPQ score was performed. Pearson correlations were obtained within and between AQ and SPQ total and individual subscale scores.

As previously discussed, dimension reduction with PCA is not ideal for data that is interrelated. Therefore, factor analysis was the primary technique in this study. In order to directly compare these data with Dinsdale et al. (35), a PCA including all nine SPQ and five AQ subscales was also conducted. The 32-items of the SPQ-BR were then extracted and a PCA with the seven SPQ-BR and five AQ subscales was conducted (35, 40). Finally, the full-scale ASQ was subjected to a factor analysis with maximum likelihood estimation. Due to the well-reported relationship between AQ and SPQ subscales, there were reasonable theoretical grounds to conduct an oblique (direct oblimin) rotation, taking into account the relationship between the factors (43). The sampling adequacy (Kaiser–Meyer–Olkin measure – KMO) of the data was found to be suitable for each analysis (AQ: KMO = 0.670; SPQ: KMO = 0.887; ASQ: KMO = 0.894; ASBQ: KMO = 0.843). Correlations between the subscales were adequate for factor analysis with Bartlett's test of sphericity significant for AQ [$\chi(10) = 387.9$, $p < 0.001$], SPQ [$\chi(36) = 1610.1$, $p < 0.001$], ASQ [$\chi(91) = 2582.3$, $p < 0.001$], and ASBQ [$\chi(66) = 1417.6$, $p < 0.001$] (43). Factors/components with Eigenvalues >1.0 were retained as substantial representations of the variation in the model, and the Scree Plot was used as visual support for the retained factors. Subscale contributions to the model were referred to as "factor loadings" and reflected the strength of the relationship between the factor/component and the subscale. Factor loadings below 0.3 were suppressed in order to report only important factor contributions (43). Pearson correlations were obtained between on the resultant factor analysis factors, total AQ, total SPQ, cognitive–perceptual, interpersonal, and disorganized scores.

RESULTS

The mean AQ and SPQ scores for males and females are shown in **Table 1**. A one-way ANOVA revealed no significant gender effects on mean AQ score [$F(1,448) = 0.557$, $p = 0.456$], however, there was a significant difference in SPQ score [$F(1,448) = 4.71$, $p < 0.05$]. Participant age did not affect AQ ($r = 0.031$, $p = 0.507$) or SPQ ($r = -0.006$, $p = 0.904$) score.

AQ AND SPQ SUBSCALE CORRELATIONS

The correlation matrix in **Table 2**, consisting of total SPQ, total AQ, and all 14 subscales, showed strong correlations between total AQ and total SPQ scores. Each individual subscale was significantly correlated with AQ and SPQ total scores; however, there was only a weak relationship between total AQ and odd beliefs (SPQ), and between total SPQ and imagination (AQ).

Among the individual subscales, the strongest relationships were between social skills (AQ) and communication (AQ) and interpersonal subscales (SPQ): social anxiety, no close friends, and constricted affect. Communication (AQ) also had a robust relationship with the disorganized subscales (SPQ): odd behavior and odd speech. Notably, there were very weak to no relationship detected between imagination (AQ) and all SPQ subscales, and between odd beliefs (SPQ) and all AQ subscales.

COMPONENT AND FACTOR STRUCTURE OF COMBINED AQ AND SPQ (ASQ)

The PCA of the nine SPQ and five AQ subscales is presented in **Table 3** below. The comparison ASQ PCA resulted in a three-component solution. The unique contribution (component loading) of each ASQ subscale to the model was reported in the Pattern Matrix, summarized in **Table 3**. Scores below 0.3 are not shown.

Table 1 | Mean gender difference in AQ and SPQ.

N = 449	*N*	AQ M (SD)	Min	Max	SPQ M (SD)	Min	Max
Male	162	17.6(6.8)	1	36	24.6(12.6)	2	65
Female	287	17.1(6.6)	1	35	21.8(12.8)	2	61

AQ, autism spectrum quotient; SPQ, schizotypal personality questionnaire; M, mean; SD, standard deviation.

Table 3 illustrates clear overlap of AQ and SPQ subscales, particularly in component 1, which included disorganized (odd behavior and odd speech), interpersonal (no close friends, constricted affect, and social anxiety), cognitive–perceptual (suspiciousness ideas of reference and unusual perceptual experiences) and AQ (communication, social skills, and attention switching) subscales. Component 2 was loaded with imagination, attention to detail, and social skills of the AQ. Finally, component 3 comprised of cognitive–perceptual subscales odd beliefs, unusual perceptual experiences, and ideas of reference, as well as attention to detail from the AQ.

The factor analysis of the ASQ, with an oblimin rotation, resulted in a three-factor solution. The pattern and structure matrix are presented in **Table 4**. The pattern matrix reports the regression coefficient for each subscale on each factor, that is, the unique contribution that each subscale has to each factor. The structure matrix on the other hand, reports the correlation coefficient between the subscale and factor, thus the factor loading of each subscale takes into account the relationship between factors.

Table 4 illustrates the clear overlap found between AQ and SPQ subscales, particularly in Factor 1. AQ subscales (communication, social skills, and attention switching) and all SPQ subscales but odd beliefs (cognitive–perceptual) loaded on Factor 1. Factor 1 will be referred to as *Social Disorganization*. Factor 2 comprised cognitive-perceptual subscales odd beliefs, unusual perceptual experiences, and ideas of reference, as well as attention to detail from the AQ, with weak contributions from suspiciousness and odd speech. These factor loadings suggest intrinsic attributes that lead to unusual perceptions, speech and behaviors, and hereafter, Factor

Table 2 | Correlation matrix for total AQ, total SPQ, and individual subscales.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Social skill															
Communication	0.501														
Attention switching	0.38**	0.41**													
Attention to detail	0.40**	0.12*	0.06												
Imagination	0.34**	0.19**	0.11**	0.29**											
AQ total	0.89**	0.67**	0.63**	0.58**	0.55**										
Ideas of ref	0.33**	0.41**	0.42**	0.16**	0.03	0.43**									
Odd beliefs	0.09	0.04	0.07	0.31**	0.03	0.17**	0.40**								
Unusual perceptual exp	0.21**	0.38**	0.34**	0.18**	−0.08	0.33**	0.56**	0.41**							
Suspiciousness	0.38**	0.42**	0.44**	0.21**	0.08	0.48**	0.63**	0.26**	0.47**						
Social anxiety	0.54**	0.50**	0.44**	0.23**	0.11*	0.57**	0.46**	0.13*	0.34**	0.45**					
No close friends	0.58**	0.48**	0.41**	0.23**	0.18*	0.58**	0.46**	0.07*	0.34**	0.51**	0.55**				
Constrict affect	0.52**	0.50**	0.32**	0.29**	0.22**	0.57**	0.38**	0.05	0.30**	0.42**	0.46**	0.62**			
Odd behavior	0.35**	0.52**	0.40**	0.08**	0.07	0.44**	0.47**	0.14*	0.42**	0.42**	0.36**	0.51**	0.45**		
Odd speech	0.31**	0.48**	0.32**	0.25**	0.10*	0.46**	0.52**	0.22**	0.50**	0.51**	0.36**	0.48**	0.50**	0.53**	
Total SPQ	0.54**	0.61**	0.52**	0.30**	0.12*	0.65**	0.79**	0.39**	0.69**	0.76**	0.68**	0.75**	0.70**	0.70**	0.75**

$*p < 0.05$, $**p < 0.001$.

Table 3 | Principal component analysis of combined AQ and SPQ subscales.

	Component 1	Component 2	Component 3
Communication	0.785		
No close friends	0.782		
Odd behavior	0.740		
Constricted affect	0.697		
Social anxiety	0.691		
Attention switching	0.683		
Suspiciousness	0.628		
Odd speech	0.625		
Ideas of reference	0.593		0.458
Social skill	0.592	0.512	
Attention to detail		0.744	0.446
Imagination		0.724	
Odd beliefs			0.884
Unusual perceptual experience	0.454		0.563
Eigenvalues	5.650	1.574	1.332
Variance explained	40.4%	11.2%	9.5%
Rotation sum of square	5.39	1.80	2.23
Total variance	61.1%		

Subscale: SPQ: AQ:

Table 4 | Factor analysis pattern and structure matrix of combined AQ and SPQ subscales.

	Pattern matrix			Structure matrix		
	F1	F2	F3	F1	F2	F3
No close friends	0.738			0.757		0.375
Communication	0.721			0.700		
Odd behavior	0.713			0.679		
Ideas of reference	0.648	0.376		0.701	0.528	
Suspiciousness	0.643			0.691	0.385	
Constricted affect	0.641			0.679		0.413
Odd speech	0.633			0.671	0.332	
Social anxiety	0.623			0.663		0.337
Attention switching	0.605			0.582		
Unusual perceptual experience	0.512	0.438		0.572	0.560	
Odd beliefs		0.721			0.716	
Attention to detail		0.361	0.664		0.330	0.642
Social skill	0.509		0.512	0.620		0.651
Imagination			0.458			0.473
Eigenvalues	5.181	1.091	0.828			
Variance explained	37.0%	7.8%	5.9%			
Rotation sum of square	5.005	1.527	1.605			
Rotation variance explained	30.0%	10.9%	9.8%			
Total variance	50.7%					

Subscale: SPQ: AQ: F, factor.

2 will be referred to as *Perceptual Oddities*. Factor 3 was loaded with imagination, attention to detail, and social skills of the AQ, with weaker contributions from constricted affect to social anxiety. Factor 3 will be referred to as *Social Rigidity*. In the subsequent discussions, the structure matrix is referred due to its representation of the relationship between the factors. It is important to note that the ASQ PCA component 2 and component 3 subscales in **Table 3** were opposite to ASQ factor analysis Factor 2 and Factor 3 subscales in **Table 4**.

The distribution of factor scores across 449 participants can be visualized easily via a RGB color additive model, where red represents Factor 1 (*Social Rigidity*), blue represents Factor 2 (*Perceptual Oddities*), and green represents Factor 3 (*Social Disorganization*) (see **Figure 1**). While individual differences in factor scores can be discerned, so can the general correlation between AQ and SPQ scores. Relative to the regression line, diametric tendencies are clearly observed with green/blue shadings to the bottom right and pink/purple/brown shades to the upper left.

Figure 1 is a visual representation of the relationship between SPQ and AQ scores for the 449 participants. The overall correlation between scores is evident through the main trend of the data points. The colors in the plot represent how each participant scored on the three factors of the Factor Analysis. It is clear that those with more *Social Rigidity* scored higher on total AQ and

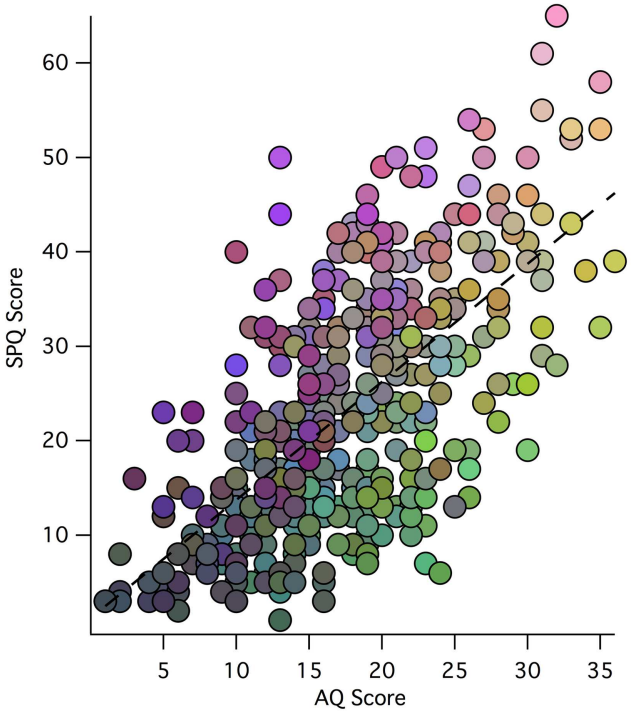

FIGURE 1 | Scatter plot of participant total SPQ vs. AQ scores: weightings of each participant's three-factor model scores is indicated by an RGB color model (scaled for each factor), where red represents Factor 1, blue represents Factor 2, and green represents Factor 3 (with the same scaling of factor values to color values for each factor). Thus, the low scores in both AQ and SPQ toward the origin tend to be shaded gray, while the extreme AQ and SPQ scores are more illuminant.

lower on total SPQ. Similarly, those with more *Perceptual Oddities* had higher total SPQ and lower total AQ. Shared *Social Disorganization* is seen along the line of best fit and into higher SPQ reflecting a relationship between the factors, and supporting the overall relationship between autism and schizophrenia spectrum disorders.

COMPARING THE PCA STRUCTURES OF THE ASQ AND ASBQ

To directly compare with Dinsdale et al. (35), we replicated the AQ and SPQ-BR subscales (ASBQ) and ran a PCA. A three-component solution was revealed, similar to our full-scale ASQ PCA, which explained 56.15% of the variance. However, there were some differences between the models (see Table S1 in Supplementary Material). The most significant change in the component structure from the ASQ to the ASBQ was the transfer of subscales no close friends and constricted affect from the ASQ component 1 to ASBQ component 2. In restricting these two subscales to one no close friends/constricted affect subscale, it fell in line with AQ subscales attention to detail, imagination, and social skills. Furthermore, social skills contributed more to component 2 than component 1 in the ASBQ compared to the ASQ PCA.

QUESTIONNAIRE AND FACTOR CORRELATIONS

Pearson correlations between participant scores on the three factors (*Social Desirability*, *Perceptual Oddities*, *and Social Rigidity*), total AQ, total SPQ, and the SPQ dimensions are shown in **Table 5**.

Strong correlations were evident between *Social Disorganization*, and AQ and all SPQ dimensions. There were strong correlations between *Perceptual Oddities*, and SPQ total and cognitive–perceptual subscales, this relationship was weak for total AQ. Finally, there was a strong correlation between *Social Rigidity* and total AQ, but weak for total SPQ. There was a weak positive relationship between *Social Disorganization*, and *Perceptual Oddities* and *Social Rigidity*, with no relationship present between *Perceptual Oddities* and *Social Rigidity*.

Table 5 | AQ and SPQ correlations with factor analysis factors.

	Social desirability	Perceptual oddities	Social rigidity
Total AQ	0.75**	0.15**	0.76**
Total SPQ	0.96**	0.51**	0.30**
Interpersonal	0.75**	0.08	0.42**
Cognitive–perceptual	0.66**	0.64**	0.08
Disorganized	0.62**	0.16*	0.07
Social desirability	–	0.3*	0.35*
Perceptual oddities	0.3*	–	−0.03
Social rigidity	0.35*	−0.03	–

*$p < 0.05$, **$p < 0.001$.

DISCUSSION

This study was the first to investigate the contributions of autistic and schizotypal traits through a combined, randomized autism schizotypal questionnaire (ASQ). We revealed a robust three-factor solution, as opposed to Dinsdale et al.'s (35) two-components, in the analysis of only shared variance between the subscales. The correlation and factor analyses provided face value support for a shared fundamental phenotype in autism and schizophrenia spectrum disorders; *Social Disorganization* (3, 5, 34, 35). Further, they exposed independent positive schizotypy and autistic rigidity phenotypes. This evidence brings to light an important question: does the relationship between autistic and schizotypal scores result from a common phenotype, or is it due simply to a lack of differentiation between distinct symptoms by measurement tools?

As expected, the first factor, *Social Disorganization,* supported a comorbid social–cognitive dysfunction central to autism and schizophrenia spectrum disorders (5, 16–19, 35). *Social Disorganization* included social AQ and all SPQ subscales but odd beliefs, explaining the majority of the variation in the subscale scores. The autism and schizophrenia spectra are presented in current diagnostic tools as completely separate disorders. Therefore, diagnosis relies on the subjective interpretation of symptoms that are specific to autism and schizophrenia spectrum disorders, excluding the shared phenotype. Clearly, relying on subjective symptom assessment risks confusion and misinterpretation, potentially leading to misdiagnosis and mistreatment of symptoms. The trait combination of the *Social Disorganization* factor is reminiscent of schizoid PD, defined by the DSM-IV-TR (12) as exclusively negative schizotypy (prior to its removal from the DSM-5). Core features of schizoid PD are fundamental to the pervasive social dysfunction in autism; lack of interest in, and active avoidance of social situations both in occupation and daily life, restricted affect and empathy, odd communication, and relationship detachment, as well as rigid pursuit of personal interests (12–14). Schizoid PD may be the conceptual or phenotypic link between autism and schizophrenia spectrum disorders, with impairments in empathy, communication oddities, social isolation, and mental rigidity some of the common central features (13, 14). Social anhedonia is another core feature of schizoid PD (24, 25, 73), the negative aspects of schizotypal PD (24, 25) and autism (26), which is characterized by atypical interpersonal behaviors. Collins et al. (24) found that social anhedonics have significantly higher scores on schizoid scales than controls; however, social anhedonics do not differ in level of schizotypy. This relationship suggests that the schizoid phenotype provides a more accurate representation of social anhedonia than does schizotypy (24). *Social Disorganization* appears to reflect the schizoid phenotype as a combination of social autistic and Interpersonal schizotypal tendencies. With the addition of disorganization in speech and behavior, *Social Disorganization* links the two spectrum disorders and raises cause for concern over the accuracy of current diagnostic processes.

Disorganized subscales of the SPQ were a substantial contributor to the *Social Disorganization* factor. Disorganization was not a specific criterion for schizoid PD; however, SPQ Disorganized subscales have explained a substantial amount of variance in the AQ, particularly in communication (5, 14) and motor behavior (14). Pervasive interpersonal dysfunction leads to disorganization in speech and behavior, which manifests in the social environment. This indirect effect provides an explanation for the role of disorganized subscales in the first factor. In addition to disorganization, cognitive–perceptual subscales contributed to the first factor, supporting broad shared traits between the disorders (3, 11, 33–35).

In both autism and schizophrenia, environmental interpretation plays an integral role in the individual's experience. Specifically, the misinterpretation of environmental stimuli is evident in both spectra and can be quantified with the SPQ subscale unusual perceptual experience, which has been found to mimic AQ predictors of abnormal sensory responses (4). Furthermore, schizoid individuals report more fantasy and heightened sensitivity experiences (14), explaining its role in the shared *Social Disorganization* factor.

The strength of the relationship between the AQ, and interpersonal and disorganized SPQ subscales, and weak relationship with cognitive–perceptual subscales, further support the underlying schizoid phenotype. These data suggest that the interpersonal and social AQ subscales scores are a reflection of each other, not differential measures of separate traits. Altogether, the correlations demonstrated a clear common *Social Disorganization* that links the two spectra, which can be defined in terms of schizoid PD.

The exclusion of schizoid PD from the DSM 5 was a consequence of little empirical research resulting in only 1% reported pathological prevalence of the disorder (13, 74). Although the diagnosis has been removed, the schizoid phenotype remains a distinct cluster of symptoms (75). The diagnostic exclusion criteria for schizoid PD; independence from schizophrenia, mood disorder with psychotic features, psychotic disorder, and pervasive developmental disorder, may have contributed to its removal from the DSM 5 (12). The very nature of the schizoid phenotype suggests that affected individuals may carry out a life that suits their social preference. Thus, seeking clinical intervention due to increasing symptom severity that is in line with more severe schizophrenia or autism spectrum pathology (13). Although schizoid PD tends to be more stable than schizotypal PD, schizoid symptoms can be prodromal to schizotypal PD, which in turn can be prodromal to more severe schizophrenia spectrum disorders (13, 14). A child presenting with profound negative symptoms (abnormal social interaction and interpersonal skills, lack of eye contact, impoverished language, and restricted range of thought and cognition) may be assigned a diagnosis of autism rather than child-onset schizoid PD, or alternate schizophrenia spectrum disorders. Furthermore, an additional schizophrenia diagnosis to pre-existing autism is possible should odd language and behavior be misinterpreted (47, 48). A diagnosis of autism relies on the individual's developmental history, and disclosure of this information could be difficult as it depends largely on the mental health of the parent (47). Relying on relatives to provide clinical information can be difficult due to the genetic association between the disorders. Schizoid, paranoid, and schizotypal PDs are more likely in relatives of schizophrenia and ASDs (12, 55). The mental health history of relatives may also lead to the symptoms classification that is in line with genetic predictions. The risk of misdiagnosis due to misinterpretation of social and communication dysfunction is accentuated by the removal of schizoid PD, incorporation of Asperger's disorder into autism, and removal of stringent age of onset and language development delay criteria in autism (10). These changes increase the variability and ambiguity in differentiating autism and schizophrenia spectrum disorders, thereby increasing diagnostic and therapeutic risks.

The second factor, *Perceptual Oddities*, separated the positive dimension of the schizophrenia spectrum from the shared *Social Disorganization* phenotype. After the relationship between the factors was taken into account, strongest contributions to this factor were from cognitive–perceptual SPQ subscales odd beliefs, unusual perceptions, ideas of reference, and weak suspiciousness. This factor provided some support for Dinsdale et al.'s (35) second component, however, with the absence of autistic subscales in the negative direction their autism-positive schizotypy axis was not supported. Disorganized odd speech loaded weakly also, adding weight to the argument of a differential schizotypal construct. Interestingly, attention to detail had a moderate contribution to *Perceptual Oddities*, as in Dinsdale et al. (35). Cognitive–perceptual features have been found to explain a substantial proportion of the variance in Attention to Detail (5), and those scoring highly may be particularly analytical of details leading to an over-interpretation of reality. Odd beliefs were the strongest contributor to *Perceptual Oddities*, and had no contribution to any other factor. Dinsdale et al. (35) found odd beliefs to be the most significant contributor to their second diametric component, suggesting that this trait may play a key role in the differentiation between autistic and schizotypal tendency. Suspiciousness, however, was not an influential predictor of *Perceptual Oddities*. Instead suspiciousness loaded substantially on the shared factor, *Social Disorganization*. The relationship between suspiciousness and *Social Disorganization* may be explained by the continual social distress, insecurities, and anxiety that lead to increased suspiciousness in children with autism, which remain to adulthood (4). The strength of the relationship between *Perceptual Oddities* and cognitive–perceptual subscales, but not total AQ, interpersonal and disorganized subscales, suggested this phenotype was specific to psychosis.

Together, the AQ subscales imagination, attention to detail, and social skills made up the third factor, *Social Rigidity*, which was exclusively autistic until the correlation between factors was taken into account. The factor correlations revealed a contribution, although weak, from all interpersonal subscales. *Social Rigidity* reflected the rigidity of thought, restricted, and repetitive behaviors, and social dysfunction that are key criteria for ASDs. This phenotypic construct was not found in Dinsdale et al.'s (35) restricted analysis. The AQ subscale imagination was only a moderate contributor to the *Social Rigidity* factor and had weak correlations across all subscales. This finding opposed the diametric model for rigidity of thought in autism and fluidity of thought in schizophrenia, as imagination was not diametric to AQ subscales (2, 5). Individuals with schizophrenia, as well as those with autism, report higher rigidity of thought as measured by imagination than controls (3, 32). This is perhaps a result of a deficit in the active control of imaginative thought in schizophrenia, while representing a lack of diversity in imagination in autism (3). Wolff et al. (14) reported high levels of fantasy in schizoid participants, but also rigidity of mental set, symptoms that are seen in schizophrenia and autism, respectively. Altogether, these imagination traits were highly reported across spectrum groups, but tap into differential thought processes, questions the specificity of the imagination subscale (32). Dinsdale et al.'s (35) data did not produce this autism-specific component, nor did their analysis of Wakabayashi et al.'s data. Instead, the autism-specific subscales loaded negatively against positive schizotypy subscales in a diametric second component, implications of which will be discussed

below. *Social Rigidity* had a strong relationship with total AQ, but a weak relationship with total SPQ and its three dimensions, thus represented more classically autistic features.

Our restricted ASBQ PCA, conducted to contrast with Dinsdale et al. (35) and factor analysis as a data reduction technique, revealed some observable differences to the ASQ PCA. First, our PCA's second and third components are in reverse to those of our factor analysis. Second, the combined and restricted constricted affect/no close friends subscale shifted from component 1 in the ASQ PCA, to component 2 in the ASBQ PCA. This shift renders the subscale more "autistic" and thereby reduces its distinction between autistic tendency and negative schizotypy. Third, the ASBQ third component was almost exclusively loaded with odd beliefs, suggesting that odd beliefs are a separate phenotype of schizotypy in the restricted model. Odd beliefs are culturally and sample sensitive (5, 12), thus it is important to specify that these data were taken from an Australian population, while Dinsdale et al. (35) took their sample from Canadian Undergraduate students. Fourth, The AQ subscale attention to detail was strongly loaded on the second component for both ASQ and ASBQ models as a diagnostically specific autistic trait. However, Dinsdale et al. (35) suggested that attention to detail represents an independent dimension of autism, as the subscale did not contribute to either component in their restricted model. Finally, the ASBQ subscales explained less of the model variance than did the ASQ. This was particularly true of Component 1, providing further support that the full-scale questionnaire is a more comprehensive assessment of autistic and schizotypal traits. Due to the differences in dimension reduction process between PCA (using unique plus shared variance) and factor analysis (only shared variance), the factor analysis subscales explained slightly less of the total variation than the subscales in PCA extraction (42, 43, 45). While PCA is a suitable tool for analyzing datasets without *a priori* assumptions about the existence of underlying constructs, we argue that the use of factor analysis here was a superior method for this type of dataset, as it exposes underlying constructs in autistic and schizotypal tendency (42, 43, 45). Thus, the three-factor model was clearly a more accurate representation of shared and differential traits.

Dinsdale et al. (35) identified a shared social–communication disinterest, impairment, and abnormality despite their use of the SPQ-BR and PCA technique. This indicates that the common *Social Disorganization* phenotype is robust across instruments. However, we argue that the full-scale ASQ factor structure provides a more comprehensive representation of autistic and schizotypal tendency, as it more accurately reflects the underlying constructs that characterize the two spectra. Furthermore, the *Perceptual Oddities* and *Social Rigidity* phenotypes were somewhat unrelated, rather than diametric. Thus, these findings provide evidence against the diametric model of autism and schizophrenia (3, 5, 33, 34) and Dinsdale et al.'s (35) diametric autism-positive schizotypy axis. The underlying constructs identified in this study supported literature reporting positive schizophrenia symptoms in autism, and autistic symptoms in schizophrenia (4, 6, 11, 33, 34). The ASQ has shown a clear separation of disorder specific traits, thus may be a useful tool for distinguishing autistic and schizotypal tendency that could be validated in the clinical setting. However, the ASBQ also extracted three factors, suggesting that it is not merely the use of the full-scale instrument that exposes the differential factors.

The inclusion of a "neutral" response option in the SPQ-BR presented by Dinsdale et al. (35) creates noise in the data that may have resulted in their diametric second component. Forcing an affirmative or negative response, as in our 4-point scale, provided better discriminant value than a scale with a "neutral" response. Furthermore, it would expose those that tend to respond in a socially desirable manner despite possessing certain trait. Wakabayashi et al. (34) presented their questionnaires separately in their original form, with the SPQ in a "yes/no" forced choice format. With only two response options and the absence of reverse scored items in the SPQ, a bias to a socially desirable "no" response is possible. Moreover, a Likert scale design has been shown to improve internal reliability and convergence of the SPQ (70). In combining the AQ and SPQ, reverse scored items are included and all items are presented on a 4-point Likert scale with the neutral response option removed, thus response bias is reduced. Consequently, these data better represented the relationship between autistic and schizotypal tendency. The self-report nature of these results provided an individual's perspective of their own behavior and personal interests, but may be subjected to social desirability bias. The response quality does however reflect a very personal representation to an individual's thoughts, feelings, and behaviors, perhaps providing a richer response quality than clinically observed behaviors. However, it is possible that retaining 4-point scale in the scores may improve the item-by-item correlations and consequently the reliability and factor analysis (76).

Altogether, with the evident confusion in behavioral overlap between social AQ and interpersonal SPQ at a trait level, which reflects schizoid PD, there is a risk of misdiagnosis in clinical settings. These data highlight the need for care in diagnostic and research settings involving the two spectra, particularly in the recruitment of accurate and distinct sample groups to avoid unbiased conclusions. As imaging research continues to identify neuromarkers specific to social–cognitive function (2, 18, 31), the search for differential neuromarkers to separate social–cognitive dysfunction that distinguish autistic and schizophrenia spectrum disorders is imperative (2, 18, 22). However, in light of the similarity in behavioral phenotypes, researchers must be vigilant to ensure exclusion of possible co-morbidities and misdiagnoses within the participant sample (1, 8, 22). Ultimately, neuromarkers are likely to provide an efficient and effective means for intervention, diagnosis and treatment development (1).

In conclusion, we presented robust evidence for a shared *Social Disorganization* phenotype in autistic and schizotypal tendency that resembles schizoid PD. In addition, we revealed discriminating factors of *Social Rigidity* and *Perceptual Oddities* that represented a specific phenotype in autistic and schizotypal tendency, respectively. This is in contrast to Dinsdale et al.'s (35) diametric component. We suggest that these discriminating factors be validated and applied in neuroimaging studies to identify neuromarkers associated with these factors. The identification of neuromarkers that differentiate autistic and schizotypal traits may ultimately lead to an objective diagnostic tool. This in turn may prevent misdiagnosis arising from the misinterpretation of shared phenotypes.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at http://www.frontiersin.org/Journal/10.3389/fpsyt.2014.00117/abstract

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Schizotypal traits are associated with poorer executive functioning in healthy adults

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Previous research has shown mild forms of the neurocognitive impairments seen in schizophrenia among healthy individuals exhibiting high schizotypal traits. This study aimed to explore associations between schizotypy and cognitive performance in an adult community sample. Ninety-five females and 79 males completed the Oxford–Liverpool Inventory of Feelings and Experiences (O-LIFE), which measures four separable aspects of schizotypy: cognitive disorganization, unusual experiences, introvertive anhedonia, and impulsive non-conformity. Subsequently, participants were administered a neurocognitive battery incorporating measures of executive skills including inhibition, cognitive flexibility, reasoning, and problem solving along with measures of attention and processing speed and both verbal and spatial working memory. In line with predictions, the current study found that higher scores on the subscales of unusual experiences, cognitive disorganization, and impulsive non-conformity related to worse performance on a measure of inhibition. Additionally, as introvertive anhedonia increased, both attention and processing speed and reasoning and problem-solving performance became more impaired. In conclusion, this study extends schizotypy literature by examining the subscales of the O-LIFE, and enables inferences to be drawn in relation to cognitive impairment in schizophrenia.

Keywords: schizotypy, schizotypal traits, psychosis proneness, cognition, executive functioning, attention, inhibition, memory

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Introduction

Schizophrenia generally a lifelong psychiatric illness associated with distressing mood, cognitive, and functional symptoms (1). Cognitive impairment is a key component of schizophrenia and is generally resistant to current treatment medications (2). In addition to an overall decrease in IQ, a range of cognitive impairments have been found to be associated with the disorder, particularly in the areas of "executive functioning," an umbrella term referring to a range of functions that include the capacity to plan, organize, attend to, monitor, and inhibit behaviors, as well as in the areas of language and memory (3). Such cognitive deficits are likely to be premorbid, that is, they precede the onset of the illness (2, 3). Additionally, they are usually stable or enduring throughout the course of the illness and often remain during symptom remission (2, 3). Cognitive impairments hinder day-to-day functioning and are one of the strongest predictors of clinical, social, and functional outcomes, even more so than positive and negative symptomatology (2, 3). Cognitive functioning is

also important to treatment decision-making and can be a good predictor of treatment effects (2).

Mild forms of the cognitive deficits observed in schizophrenia are also found in unaffected first-degree relatives and healthy individuals exhibiting schizotypal traits (4, 5). This has led recent studies to suggest several cognitive measures as potential "endophenotype candidates" or biological markers for the illness (3–5). Schizotypy is a psychological construct involving personality characteristics and perceptions, beliefs, and experiences that are phenomenologically similar to, but less severe than the symptoms of schizophrenia (6, 7). Consequently, schizotypy represents a major focus area of research on schizophrenia and the dimensional approach to it (8). By studying schizotypy in the general population, predisposing and potentially protective factors for schizophrenia can be explored, without the potential confounds of symptoms, motivation deficits, illness chronicity, and treatment medications (9). Recent literature has suggested that schizotypy can be broken down into four factors, which reflect those symptom factors seen in schizophrenia (10).

Positive schizotypy taps into perceptual aberrations, magical thinking, unusual experiences, and hallucinations, and is thought to resemble positive symptomatology in schizophrenia (7, 8). Negative schizotypy encompasses introvertive anhedonia, in particular, a lack of social and physical enjoyment and an avoidance of social connections, which is suggested to reflect negative symptomatology (7, 8). Cognitive disorganization taps into deficits in decision-making abilities, concentration, attention, language, and thought disorder (7, 8). Lastly, asocial behavior taps into impulsive non-conformity, such as reckless, harmful, or disinhibited behaviors (7).

Poorer neurocognitive performance similar to that seen in schizophrenia, albeit in a milder form, has been identified in individuals exhibiting high levels of schizotypy traits (11). For example, inferior levels of attention and executive functioning have been revealed: Cimino and Haywood (12) found healthy individuals high in schizotypy traits, based on a mean of all Oxford–Liverpool Inventory of Feelings and Experiences (O-LIFE; a self-report inventory assessing schizotypy) factor scores, to exhibit significantly more errors and longer latencies on the Stroop Color–Word Interference Test, in comparison with individuals low in schizotypal traits. This finding is indicative of relative impairments in inhibition and attentional switching or cognitive flexibility (12). However, findings of cognitive disinhibition in schizotypy have not always been consistent. For example, some studies have found no significant associations between schizotypy factors and Stroop Color–Word Interference Test performance (13, 14). Conversely, using the Wisconsin Card Sorting Test (WCST), both Gooding et al. (11) and Kim et al. (15) revealed comparative deficits in cognitive flexibility in university students exhibiting high levels of schizotypal traits. This was evidenced by fewer categories achieved and increased preservative errors compared with controls (11, 15).

Additionally, further evidence for poorer performance in attention and executive functioning has been identified by past research. Using the O-LIFE in a university sample, Rawlings and Goldberg (16) revealed a significant association between positive schizotypy and decreased sustained attention, as evidenced by a positive relationship between the cognitive disorganization factor of the O-LIFE and poorer performance on the Continuous Performance Task. Chen et al. (9) had similar findings, however, also found an association between negative schizotypy and poor performance on the Continuous Performance Task.

Relative deficits in verbal and spatial working memory have also been identified by previous research. For instance, using a university sample, Matheson and Langdon (17) found that once age was controlled for verbal working memory, as evidenced by correct manipulations on the Letter–Number Sequencing Task, was a significant predictor of cognitive, perceptual, and negative interpersonal schizotypal traits. Similar associations between schizotypy and spatial working memory have also been revealed by previous studies (18). However, findings between working memory and schizotypy have not always been replicated, for example, Lenzenweger and Gold (19) did not identify a significant relationship between positive schizotypy and verbal working memory (Letter–Number Sequencing Task).

Only a small number of studies have examined cognitive functioning in relation to separate schizotypy factors. These studies suggest that lowered performance in attention, executive functioning, and sustained attention (using a Continuous Performance Task) is related to higher scores on the cognitive disorganization schizotypy factor as well as negative schizotypy (9, 16).

Taken together, these findings suggest that high schizotypy is associated with reduced cognitive ability (albeit milder than that seen in schizophrenia). However, this is a very broad finding and more fine-grained analysis of the nature of this relationship is required. As discussed, there are currently only a small number of articles examining the schizotypy subtypes (9, 16). Furthermore, past schizotypy research has predominantly relied upon adolescent or university educated samples who are unlikely to be a good match to the schizophrenia population generally. By using a sample of adults over the average age for schizophrenia onset, it is assumed that the schizotypal traits exhibited by individuals are likely to lie within healthy limits and therefore are not dormant symptoms of psychopathology (20). Additionally, previous literature has identified first-degree relatives of patients with schizophrenia to score significantly higher and with more variation for both positive and negative schizotypy compared with controls (21). Consequentially, by using extensive exclusion criteria that restricts the presence of individuals with a current psychiatric illness or with a family history of a schizophrenia spectrum disorder or bipolar disorder, the dormant symptoms of psychopathology are further controlled for and the sample is therefore likely to be more homogenous in regards to schizotypal traits. Lastly, due to primarily small sample sizes in previous studies, the need for the exploration of the association between schizotypy and cognition and a large sample is evident.

Based on shortcomings in the literature, the current study aimed to explore the relationship between the four-schizotypy factors defined in the O-LIFE and those areas of cognition, which have previously been found to relate to schizotypy (inhibition, cognitive flexibility, attention, processing speed, and reasoning and problem solving) using traditional neurocognitive tasks. This study will address previous limitations by (a) looking at the relationship between individual schizotypy factors of the O-LIFE and

cognition, (b) using a large sample, (c) over the typical age for schizophrenia onset, and (d) free from genetic liability and current psychopathology.

Given previous findings of inhibitory deficits in schizophrenia patients and high schizotypy samples, it was hypothesized that higher scores on the unusual experiences and cognitive disorganization factors of the O-LIFE would relate to poorer inhibition and cognitive flexibility, as measured by the Color–Word Interference Test performance. Additionally, in line with previous schizotypy literature, it was predicted that the introvertive anhedonia factor of the O-LIFE would negatively associate with reduced attention and processing speed, as measured by the Trail Making Test – Part A. Furthermore, it was hypothesized that there would be a negative association between the unusual experiences, introvertive anhedonia and impulsive non-conformity factors, and reasoning and problem-solving performance, as measured by a Mazes task. Lastly, based on previous findings in working memory and schizotypy, a negative relationship was also expected between both the unusual experiences and introvertive anhedonia factors, and verbal and spatial working memory performance, as measured by the Letter–Number Sequencing and Spatial Span Tasks. Furthermore, exploratory analyses of the four-schizotypy factors and all neurocognitive variables will be conducted.

Materials and Methods

Participants

Potential participants voluntarily responded to advertising through flyers at local community centers and the researcher's private social media pages. Following telephone screening, 175 healthy adults between 18 and 64 years of age (95 women and 79 men) met participation inclusion criteria. Participants were excluded from the study if they had a current psychiatric illness; history of or first-degree biological relative with schizophrenia or schizoaffective disorder; current use of a psychotropic drug; or, history of substance abuse or neurological illness. Demographic information revealed that one included participant was adopted (hence, knowledge of their biological relatives' psychiatric history was unknown), and one participant was color blind. The participant who was color blind was excluded from all color–word interference tasks. All participants were financially reimbursed for their time and travel costs. The Alfred Health Human Ethics Committee and the Monash University Standing Committee on Ethics in Research in Humans approved all experimental procedures and informed written consent was obtained by all participants in accordance with these ethical requirements.

Materials

Screening Interview

The Mini-International Neuropsychiatric Interview (M.I.N.I.), a clinician-rated brief structured psychiatric interview compatible with DSM-IV diagnostic criteria, was used to screen for the presence of psychiatric conditions (22).

The Montgomery Äsberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale, was used to assess the presence and severity of depressive symptoms, relating to the previous week (23). Items are scored on a six-point Likert scale (0–5) and summed to calculate a total score ranging from 0 to 50, with higher scores indicating greater depression severity (24).

The Wechsler Test of Adult Reading (WTAR) included to provide an estimate of intellectual functioning and premorbid verbal intelligence (25).

Schizotypy Assessment

The Oxford–Liverpool Inventory of Feelings and Experiences (O-LIFE) is a self-report questionnaire designed to measure psychosis-proneness, principally schizotypy in healthy individuals (8). The questionnaire consists of four scales: unusual experiences comprise 30-items and reflect positive symptomatology, for example, "Do you believe in telepathy?" Cognitive disorganization consists of 24-items and reflects cognitive deficits and thought disorder, for example, "Is it hard for you to make decisions?" Introvertive anhedonia comprises 27-items and reflects negative symptomatology, for example, "Do you prefer watching television or going out with people?" Lastly, impulsive non-conformity reflects a-social behavior and consists of 23-items, for example, "Do you at times have an urge to do something harmful or shocking?"

Inhibition and Cognitive Flexibility Assessment

The Delis–Kaplan Executive Function System (D-KEFS), Color–Word Interference Test, assesses inhibition and switching or cognitive flexibility (25, 26). The test consists of four conditions, each comprising 40-items: condition 1 requires respondents to name patches of color. In the second condition, respondents are required to read color names written in black ink. The third condition requires respondents to name the dissonant ink color that words are written in. In the fourth condition, respondents are required to switch between naming the dissonant ink color and reading the words. Each condition is timed and both self-corrected and unknown errors are summed for each condition to calculate a score for both raw time and total errors, ranging from 1 to 40, with higher scores indicating greater number of errors (25, 26).

For this study, the four variables of interest were: Inhibition V Color Naming raw time, which was a measure of inhibitory latency, once baseline color naming was controlled for by subtracting the raw seconds required for the first condition from the third condition; Inhibition/Switching V Inhibition raw time that was a score of cognitive flexibility or attentional switching, after inhibition was controlled for by subtracting the seconds score of the third condition from the fourth condition; Inhibition/Switching V Color Naming raw time, which was a measure of inhibitory latency and cognitive flexibility, once color naming was controlled for by subtracting the seconds required for the first condition from the fourth condition; and Inhibition/Switching V Word Reading raw time that was a measure of inhibitory latency and cognitive flexibility, after baseline wording reading was controlled for by subtracting the seconds taken for the second condition from the fourth condition.

Attention and Processing Speed Assessment

The Halstead–Reitan Neuropsychological Test Battery (HRB), *Trail Making Test – Part A*, was designed to measure attention and processing speed (27). The task requires participants to connect 25

numbers in ascending order that are randomly arranged on a page within an assigned maximum time of 300 s (27). Prior to formal task administration, participants first complete a sample exercise containing eight numbers (27). Administration of the task takes approximately 5 min and the completion time in seconds for the formal component is used as a total score with the number of errors expressed also being recorded (27).

Reasoning and Problem Solving Assessment

The Neuropsychological Assessment Battery (NAB) – Mazes assesses executive functioning, particularly planning and organization (28). The task requires participants to trace their way through a series of seven mazes of increasing difficulty (28). The time limit for each maze varies with the difficulty level and ranges from 30 to 240 s (28). Mazes are scored based on completion and response speed, with scores ranging from 0 to 26, with higher scores indicating better performance (28).

Working Memory Assessment

The Wechsler Memory Scale – Third Edition (WMS-III) – Letter–Number Sequencing assesses verbal working memory (29). The task requires the researcher to read a series of numbers and letters and the participant is required to recite the digits back to the researcher, numbers first in ascending order followed by letters in alphabetical order, with the lists increasing in difficulty (29). The task consists of 24 trials and each correct recitation receives a score of one, with individual scores summed to calculate a total score ranging from 0 to 24, with higher scores indicating better working memory performance (29).

The WMS-III – Spatial Span assesses spatial working memory and consists of two conditions: forwards and backwards (29). The first condition, forwards, consists of 16 trials and requires the researcher to touch the blocks on the Spatial Span board in an order in which the participants must repeat, with increasing difficulty (29). The second condition, backwards, again consists of 16 trials and participants are required to touch the blocks in the reverse order to that of the researcher, with increasing difficulty (29). Each correct trial obtains a score of 1, with individual scores summed to calculate a total score for each condition, ranging from 0 to 16 (29). Condition scores are then summed to calculate an overall total score ranging from 0 to 32, with higher scores indicating better working memory performance (29).

Procedure

Following a basic telephone assessment of eligibility, participants completed a demographic questionnaire and the O-LIFE. Subsequently, a brief screening interview took place, consisting of the M.I.N.I. screen and the MADRS. The neurocognitive battery was then administered successively, with counterbalancing used to reduce order effects and fatigue.

Results

Data Analysis

All raw scores were processed using PASW Version 18 (SPSS Ltd.) to produce the summary data. Although statistical analyses were based on previous literature, due to multiple comparisons, the alpha level for all statistical analyses was set at 0.01, unless otherwise stated.

Prior to analyses, assumption testing was conducted to assess the suitability of the data for a correlation analysis. Following inspection of the Frequency Table, it was found that a small percentage of data was missing from each of the variables (<5% per variable); cases were therefore excluded pairwise for all further statistical analyses. Kolmogorov–Smirnov normality tests revealed that the data violated this assumption and consequently non-parametric tests (Spearman's rho) were used for all additional analyses.

Demographics

There were no significant associations between age, years of education, verbal intelligence and depression, as evidenced by the WTAR, MADRS depression scores (see **Table 1** for descriptive statistics of the demographic variables; see the Supplementary Material for results of the Spearman's Rho analyses for neurocognitive variables by schizotypy factors) schizotypy factors scores and the neurocognitive variables ($p = 0.017$–0.908). Consequently, these variables were not controlled for in further analyses.

Descriptive Statistics and Schizotypy Factor Scores

The descriptive statistics for all neurocognitive variables are presented in **Table 2**. This table reveals the highest schizotypy factor scores to be for cognitive disorganization and impulsive nonconformity.

To further explore relationships between schizotypy factors and neurocognitive variables, a two-tailed Spearman's rho correlation analysis was conducted and results are presented below.

Inhibition and Cognitive Flexibility

In terms of assessing inhibition, the analysis revealed a significant positive association between unusual experiences and inhibition versus color naming raw time [$r_s(164) = 0.333$, $p = 0.000$], inhibition/switching versus color naming raw time [$r_s(166) = 0.347$, $p = 0.000$], and inhibition/switching versus word reading raw time [$r_s(166) = 0.345$, $p = 0.000$], accounting for 11.08, 12.04, and 11.90% of shared variance, respectively.

The Spearman's rho analysis also revealed a significant positive relationship between cognitive disorganization and inhibition versus color naming raw time [$r_s(164) = 0.21$, $p = 0.007$], inhibition/switching versus color naming raw time [$r_s(166) = 0.24$, $p = 0.002$], and inhibition/switching versus word reading raw time [$r_s(166) = 0.258$, $p = 0.001$], accounting for 4.41, 5.76, and 6.66% of shared variance, respectively. The analysis

TABLE 1 | Descriptive statistics for demographic variables.

	Mean	SD	Min	Max
Age	34.05	13.66	18	64
Years of education	16.27	2.83	9	27
WTAR scaled score	112.30	8.11	83	129
MADRS	1.79	3.01	0	26

WTAR, Wechsler Test of Adult Reading; MADRS, Montgomery Äsberg Depression Rating Scale.

TABLE 2 | Descriptive statistics for all neurocognitive variables and schizotypy factors.

	N	Missing *N*%	Mean	SD	Range	TR
O-LIFE						
Unusual experiences	171	2.3	4.98	4.86	0–25	0–30
Cognitive disorganization	171	2.3	7.22	5.24	0–20	0–24
Introvertive anhedonia	170	2.9	4.16	3.63	0–20	0–27
Impulsive non-conformity	172	1.7	7.20	4.13	0–19	0–23
D-KEFS Inhibition V Color Naming	168	4	10.54	8.21	−5 to 37	–
D-KEFS Inhibition/Switching V Inhibition	170	2.9	5.88	7.47	−12.4 to 28.20	–
D-KEFS Inhibition/Switching V Color Naming	170	2.9	12.81	11.60	−4 to 49.6	–
D-KEFS Inhibition/Switching V Word Reading	170	2.9	14.89	14.69	−4 to 57	–
Trail Making Test – Part A	173	1.1	25.56	8.91	11–68	300 s
Mazes	172	1.7	10.61	5.65	3–26	0–26
Letter–number sequencing	173	1.1	16.79	2.59	10–24	0–24
Spatial span backwards	175	0	8.95	1.80	2–14	0–16

Range, observed range of scores; TR, theoretical range of scores; O-LIFE, Oxford–Liverpool Inventory of Feelings and Experiences; D-KEFS, Delis–Kaplan Executive Function System. D-KEFS variables are measured in raw seconds.

also identified a non-significant positive trend between cognitive disorganization and inhibition/switching versus inhibition [$r_s(166) = 0.189$, $p = 0.014$].

Additionally, the exploratory analysis showed a significant positive association between impulsive non-conformity and inhibition versus color naming raw time [$r_s(165) = 0.450$, $p = 0.000$], inhibition/switching versus color naming [$r_s(167) = 0.453$, $p = 0.000$], and inhibition/switching versus word reading [$r_s(167) = 0.433$, $p = 0.000$], which accounted for 20.25, 20.52, and 18.75% of shared variance, respectively. Furthermore, a non-significant positive trend was identified between impulsive non-conformity and inhibition/switching versus inhibition [$r_s(167) = 0.168$, $p = 0.030$].

Attention and Processing Speed

In regards to attention and processing speed, the Spearman's rho analysis showed a significant positive relationship between introvertive anhedonia and Trail Making Test – Part A [$r_s(168) = 0.26$, $p = 0.001$], accounting for a small amount of shared variance (6.76%).

Reasoning and Problem Solving

In respect to planning and organization, a significant negative relationship between introvertive anhedonia and mazes raw score [$r_s(168) = -0.212$, $p = 0.006$] was revealed by analysis that accounted for a small amount of shared variance (4.49%). Conversely, analysis also showed a significant positive association between impulsive non-conformity and mazes raw score [$r_s(170) = 0.299$, $p = 0.000$], accounting for a small percentage of shared variance (8.94%).

Working Memory

In relation to working memory measures, the analysis revealed a non-significant positive trend between unusual experiences and letter–number sequencing raw score [$r_s(169) = 0.143$, $p = 0.064$]. Moreover, exploratory analysis identified a positive non-significant trend between cognitive disorganization [$r_s(175) = 0.152$, $p = 0.051$], impulsive non-conformity [$r_s(175) = 0.161$, $p = 0.038$], and spatial span backwards raw score, which accounted for a small percentage of shared variance, 2.31 and 2.59%, respectively.

Discussion

The current study aimed to explore associations between schizotypy factors and cognition in an adult community sample. The key findings from this study were significant positive associations between unusual experiences, cognitive disorganization, and impulsive non-conformity and inhibitory latency and cognitive flexibility on the Color–Word Interference Test, once baseline color naming and word reading were controlled. Additionally, findings revealed a significant positive association between introvertive anhedonia and attention and processing speed on the Trail Making Test – Part A. Lastly, results showed a significant negative association between introvertive anhedonia and reasoning and problem solving on the mazes task and a significant positive relationship between impulsive non-conformity and reasoning and problem solving on the mazes task.

Our findings of associations between positive, cognitive, and asocial schizotypal traits and impairments in inhibition and cognitive flexibility or attentional switching (Color–Word Interference Test) are in line with past studies that have found high schizotypes to display greater inhibitory latency and less accurate responses compared with low schizotypes on all inhibition and switching conditions of the Color–Word Interference Test (12). These findings are also in line with recent schizophrenia research, which has revealed inhibitory deficits using the Color–Word Interference Test (30). However, while the schizophrenia literature frequently reports a relationship with inhibitory deficits, negative symptoms are often related to inhibition, rather than positive symptoms (30). Albeit non-significant, results identified positive trends toward relationships between cognitive disorganization and impulsive non-conformity and cognitive flexibility, once baseline inhibition was controlled.

Furthermore, our results of a relationship between negative schizotypal traits and reduced attention and processing speed are consistent with past research reporting an association between negative and cognitive schizotypal traits and poorer sustained attention, as measured by the Continuous Performance Task, in a community sample (9). Similarly, these findings are in line

with previous schizophrenia research that found patients to score significantly lower on the Continuous Performance Task compared with controls (31).

Additionally, the current study found a significant negative association between introvertive anhedonia and completion time on a mazes task, suggesting that higher levels of negative schizotypy are related to poorer reasoning and problem-solving performance. This is consistent with previous schizophrenia research that found patients to demonstrate significant impairment on a mazes task in comparison with controls (32). In contrast and somewhat counter intuitively, current results also revealed a significant positive association between impulsive non-conformity and superior reasoning and problem-solving performance. One potential explanation for this inconsistent finding is that faster task commencement times associated with impulsivity may have aided in participants' increased mazes scores. In comparison with other mazes tasks, the current task did not penalize participant's performance when they entered into a "blind alley." For instance, the Porteous Maze task records a trial as unsuccessful if such behavior takes place (25). The current participants are likely to have benefited from the added speed associated with impulsivity without being punished for this commonly committed error.

Limitations

A couple of noteworthy methodological shortcomings exist in the current study. For instance, schizotypy factor scores identified in this study were below current normative scores for the O-LIFE inventory (8). Due to the restricted range of schizotypy scores in the current sample, it is possible that relationships between schizotypy factor scores and neurocognitive variables may have been revealed using a sample with a larger spread of schizotypy scores.

In addition, previous literature has suggested the use of illicit drugs to impact both schizotypy scores and cognitive performance, particularly inhibition (33). Although the current study did exclude participants if they met criteria for a current substance disorder based on the M.I.N.I. screen, it did not, however, evaluate or control the current use of illicit drugs that were not severe enough to meet this criteria. As current use of cannabis can result in healthy individuals to mimic inhibitory impairments seen in schizophrenia, controlling the use of such substances may have been beneficial.

Conclusion

In conclusion, the current study was one of the first in schizotypy literature to tease apart the relationships between factor scores and cognition in an adult community sample that accounted for psychiatric illness and family history. This allowed for the exploration of both cognitive functioning and potential compensatory mechanisms in individuals who have passed the peak onset times for developing schizophrenia. Findings from the current study further extend a limited body of schizotypy literature that enables inferences to be drawn in relation to the cognitive deficits seen in schizophrenia, without the potential confounds of illness chronicity and treatment medications. A better understanding of cognitive performance in schizophrenia is essential due to the vast experience of cognitive deficits and resistance to current treatment medications. Consequently, this research has potential practical implications for aiding in the establishment of treatments, to be used in conjunction with antipsychotic medication, for the cognitive symptoms of schizophrenia.

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Supplementary Material

The Supplementary Material for this article can be found online at http://journal.frontiersin.org/article/10.3389/fpsyt.2015.00079/abstract

Table S1 | Spearman's rho for neurocognitive variables by schizotypy factors.

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Alcohol and relatively pure cannabis use, but not schizotypy, are associated with cognitive attenuations

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Elevated schizotypy relates to similar cognitive attenuations as seen in psychosis and cannabis/polydrug use. Also, in schizotypal populations cannabis and polydrug (including licit drug) use are enhanced. These cognitive attenuations may therefore either be a behavioral marker of psychotic (-like) symptoms or the consequence of enhanced drug use in schizotypal populations. To elucidate this, we investigated the link between cognitive attenuation and cannabis use in largely pure cannabis users (35) and non-using controls (48), accounting for the potential additional influence of both schizotypy and licit drug use (alcohol, nicotine). Cognitive attenuations commonly seen in psychosis were associated with cannabis and alcohol use, but not schizotypy. Future studies should therefore consider (i) non-excessive licit substance use (e.g., alcohol) in studies investigating the effect of cannabis use on cognition and (ii) both enhanced illicit and licit substance use in studies investigating cognition in schizotypal populations.

Keywords: polydrug use, licit drug use, cognition, schizotypy, psychosis-proneness

INTRODUCTION

Cannabis sativa (marijuana) is currently the most widely used illegal substance in Europe (1). Past year cannabis use was reported by about 11.2% of all 15–34 year olds (1). This elevated prevalence rate (when compared to other illicit drug use) is concerning, because cannabis use might go along with both cognitive attenuation (2, 3) and mental health problems, in particular psychosis (4–9). Yet, only a minority of cannabis users (CU) will develop psychotic illnesses (5–7, 10). Therefore, other factors likely influence adverse consequences associated with cannabis use (9, 11).

Here, we focused on the supposedly negative implications of cannabis use on cognitive functioning while accounting for individuals' schizotypy and associated licit drug use. We did so based on the following reasoning. On the one hand, relatively pure CU (i.e., no regular drug use other than marihuana, cigarettes, or alcohol) have attenuated cognitive functioning compared to non-users (3), e.g., in verbal working memory (12), verbal short-term memory (13), and mental flexibility (3, 14). On the other hand, as detailed below, schizotypal personality features are not only part of the psychosis dimension but also associate with cognitive attenuations, cannabis use, as well as licit drug use.

The schizotypy approach assumes that psychotic symptoms exist along a continuum, with severest symptoms occurring in schizophrenia and mild sub-clinical ones in schizotypal individuals from the general population (15). Schizotypy is commonly assessed using self-report questionnaires (16, 17). Scores on these questionnaires can be commonly divided into symptom dimensions known from patients, e.g., consisting of positive schizotypy (e.g., magical thinking, unusual experiences), negative schizotypy (e.g., anhedonia), and cognitive disorganization [e.g., odd speech and behavior; (16, 18)]. When it comes to laboratory measures, high as compared to low schizotypes yield relatively impaired cognitive performance, e.g., in working memory (19, 20), cognitive flexibility (21), and verbal short-term memory (22, 23). Most relevant to our reasoning, high schizotypy goes along with elevated substance use of, e.g., cannabis (24–28), nicotine, and alcohol (26, 29). Similarly, an elevated drug use has been reported in schizophrenia when compared to healthy controls (2, 6, 30–34).

Given the above described interrelationships, it is possible that the link between cannabis and cognition is influenced by individuals' schizotypal features and/or additional licit drug use. The latter reasoning is particularly likely given that CU show higher consumption of nicotine and/or alcohol when compared to non-users (35, 36). Studies that assessed all three variables (cognition, cannabis use, and schizotypy) found that CU showed both worse cognitive performance and higher schizotypy scores (24, 37), and that only in CU schizotypal symptoms correlated with worse cognitive performance (37). When it comes to licit drug use, the available information is even scarcer, as these studies did not report on a potential effect of licit (nicotine, alcohol) drug use (24, 37). We therefore investigated the link between cognitive attenuation and cannabis use in largely pure CU and non-cannabis users (nCU), accounting for the potential additional influence of both schizotypy and licit drug use (alcohol, nicotine).

We expected that both illicit and licit drug use might be more important than schizotypy to explain variance in cognitive performance (38–40). If schizotypy would additionally or instead explain variance in cognitive performance, we would expect

the cognitive disorganization dimension (25–27) and/or positive schizotypy dimension (24, 41, 42) to be more relevant than the negative schizotypy dimension (27, 37, 42–44) that frequently resulted in heterogeneous findings.

MATERIALS AND METHODS

PARTICIPANTS

We recruited participants via advertisements looking for both pure CU (see also screening section) and non-nicotine consuming nCU. Advertisements were distributed at the local University and its vicinity on paper and electronically. We also used a local website ("Gumtree"). We recruited 83 healthy native English-speaking participants [35 CU (23 males) and 48 nCU (20 males)]. Participants either received monetary compensation for travel expenses or course credits. The University of Bristol ethics committee approved this study. All participants provided written informed consent prior participation.

SCREENING

In both groups (CU, nCU), people were excluded if they reported excessive alcohol use (>50 units of alcohol/week for men, >35 units of alcohol/women), alcohol use within 12 h prior to testing, a neurological, psychological, or psychiatric history, or visual problems (including dyslexia). Prior to study inclusion, participants were alerted that we would ask for a urine sample for drug screening. We then asked about illegal substance use within the past 3 months. To encourage honest responding, volunteers were kept unaware of the drug spectrum assessed with the urine test (it detected cannabis metabolites until about 2 weeks after its consumption). To ensure recruitment of largely pure CU, participants were excluded if they indicated regular illicit drug use (apart from cannabis) in the past 3 months (more than twice) and/or use within 2 weeks prior testing. Participants were also asked about their cannabis and nicotine use habits (e.g., average amount of times cannabis used/cigarettes per week) in the past 30 days prior testing. Data with a negative drug test were not excluded if CU self-reported occasional use (on average 1–2 times/week within the past 30 days), and/or indicated regular or frequent use (on average >2 times/week in the past 30 days), but not within the past 2 weeks (45). If regular or frequent CU indicated use within the past 2 weeks, participants with a negative drug test were excluded from further analysis. The healthy nCU were excluded if they reported nicotine and cannabis use in the past 30 days, and if they showed a positive drug test.

PROCEDURE

Participants were firstly screened by means of the procedure outlined above. Subsequently, participants came to the local department for a 1 h testing session. The CU were asked to abstain prior testing from (i) cannabis use at least 2 h and (ii) nicotine use 30 min. We chose this abstinence period for cannabis, because general psychotropic effects seem to taper off 2–3 h post-consumption (46). In the case of nicotine, acute effects on cognition seem observable within 15–35 min of nicotine consumption [e.g., Ref. (47, 48)]. After having provided written informed consent, participants underwent the urine test before continuing to the testing session. Participants first completed the drug and schizotypy questionnaires, before performing the cognitive tasks. Participants performed the tasks outlined below as well as a handedness questionnaire and a lateralized lexical decision task. Results from the latter will be presented elsewhere. Task order was randomized between participants. Finally, participants were debriefed and reimbursed for their time.

QUESTIONNAIRES

Schizotypy

The Oxford-Liverpool Inventory of Feelings and Experiences (17, 49) is a 159-item self-report instrument consisting of the following sub-scales: positive schizotypy (unusual experiences = UnEx, 30 items), negative schizotypy (Introvertive Anhedonia = IntAn, 27 items), and cognitive disorganization (= CogDis, 24 items). Finally, 23 items assess impulsive non-conformity (ImpNC). Normative values can be found in Mason et al. (17, 49). We did not account for IntAn and ImpNC in this study, because of the heterogeneity in findings in the former case (see Introduction) and because ImpNC does not represent a schizotypy dimension (17).

Drug questions

Participants reported on their prior drug use (lifetime, past year, and past month drug use), e.g., their alcohol, cigarette, cannabis, cocaine, amphetamine, hallucinogen, opiate, and prescribed drug use. Items were taken from the national household survey on drug abuse (50). This questionnaire taps into seven DSM-IV criteria for drug dependence (past 12 months) by asking if people (1) spent a lot of time obtaining, using, or recovering from the drug, (2) experienced a marked increase in amount and frequency of drug use, (3) experienced a marked decrease in the drug effect, and (4) gave up or reduced important social, occupational, or recreational activities due to drug use. It also asks if people experienced (5) drug-induced psychological problems (such as depressive mood), (6) drug-induced physical problems, and (7) a persistent desire for the drug or unsuccessful attempts to stop drug use. For each positive answer, participants received 1 point (maximum score 7) with higher values indicating higher substance use severity. Participants also indicated the average amount of joints/cigarettes per week they used within the past 30 days. For this reason, it is possible that current non-smokers (no tobacco use within the past month) receive a nicotine severity score $\neq 0$ if they have smoked within the past 12 months (this only concerned 2 of the 48 non-smokers).

BEHAVIORAL MEASURES: COGNITIVE FUNCTIONING

Trail making task

The trail making task (TMT) assessed executive functioning (51, 52). In the TMT A, participants connected numbered circles in chronological order (1–25) by drawing a line, as fast as possible. In the subsequent TMT B, participants saw circles containing numbers or letters. They drew a line as quickly as possible in chronological order switching between numbers and letters, i.e., from 1 to A, from A to 2, from 2 to B, etc. The RT for both versions was recorded. The TMT-index (RT version B minus version A) was used as an estimate of cognitive flexibility (53). Norm values are available from Tombaugh (54).

Verbal short-term memory (story-recall/logical memory)

We used a subtest of the revised version of the Wechsler adult intelligence scale (55). The experimenter read out a 60 words story. The participant was asked immediately afterwards to recall as many details as possible (maximum of 23 possible points). Normative data for young adults and university samples can be found in Bowden et al. (56) and Ivison (57), respectively.

Verbal working memory (two-back task)

Comparable to previous reports (58, 59), participants saw 64 sequentially presented digits (ranging from 1 to 9) in the middle of the computer screen (white on black background, font Arial, size 16). Participants had to press a given response key when the current digit (n) was identical to the digit n-2 (target trials). In all non-target trials, participants had to press another response key. Response key allocation was counterbalanced between participants. A third of the trials ($n = 20$) were target trials, and the remaining trials were non-target trials [$n = 44$; e.g., 59]. To increase task difficulty, we added intrusion trials. These were included to prevent restarting memorization after each successful target identification. Consequently, targets could occur twice in a row. Each stimulus appeared for 2000 ms, with an inter-stimulus interval of 500 ms (60) before the next digit appeared. Participants had to respond within 2500 ms, otherwise the trial was counted as an omission. All participants performed 16 practice trials. We measured the percentage of the correctly identified targets, as well as mean RTs for correct trials (59, 61).

As an additional note, we also measured a computerized Go NoGo task. Due to an overall ceiling performance, we omitted this task from further analysis.

DATA ANALYSIS

To determine if cannabis use affects cognitive functioning, we conducted separate univariate ANOVAs with group (CU, nCU) as between-subjects factor on the following measures: percentage of correct responses [(number of correctly identified target stimuli × 100)/total of targets] and RT in the two-back task, TMT-index, and the percentage of correctly identified units in the story-recall task [(number of correctly identified units × 100)/total of units)].

To determine effects of drug use and schizotypy on cognition, we firstly investigated the demographic characteristics of our population. We found sex differences between drug groups (see Results for details). We then correlated all variables with the outcome measures to preselect variables for the regression model (see Results for details). Neither age nor schizotypy significantly correlated with the cognitive measures. Due to the previous literature (see Introduction), we nevertheless kept UnEx scores and CogDis scores for the hierarchical regressions as follows: sex was entered in the first step, schizotypy (UnEx scores, CogDis scores) in the second step, and drug use severity (nicotine, alcohol, and cannabis) in the third step. Severity was preferred over frequency due to the former measure's relevance to clinical addiction. Exploratory analysis confirmed that drug use severity was more important than drug use frequency in the current regression analyses. Thus, three blocks of predictors were entered in nested blocks, meaning that each subsequent block contained all prior predictors and the additional predictors from the current block. Presentation of results only includes the new predictors entered, for economy of presentation. All tolerance values were above 0.2 (62) and all independent variables were mean-centered. Thus, multi-collinearity between the independent variables was considered negligible. The dependent variables were (i) percentage correctly identified targets and mean RT for correctly identified targets and non-targets in the two-back task; (ii) TMT-index; and (iii) percentage of correctly recalled units in the story-recall task.

Kolmogorov–Smirnov tests for the groups separately revealed normal distribution for all behavioral measures. All p-values were two-tailed and the α-level was set at 0.05.

RESULTS

PARTICIPANTS

We identified 35 CU (out of 83 healthy native English-speakers). On average (±SD), CU smoked 11.14 joints per week (±12.16), a frequency that can be classified as heavy use [>5 joints per week; (63)]. The last cannabis consumption was on average more than 24 h ago (114.37 ± 143.02 h) with 4 CU reporting cannabis use 2–6 h before testing. When only individuals are considered whose last cannabis consumption was more than 6 h ago, the results stayed largely the same. Age of cannabis use onset was at 15.46 years of age (±1.87 years). Within the CU group, 13 individuals were educated to college level (37%), 1 to secondary school (3%), and 21 to university degrees (60%). Of the 48 nCU, 12 individuals had college degrees (25%) and 36 had university degrees (75%). A chi-square test indicated that the two groups did not differ from each other in terms of highest finished education level [$\chi^2(\mathrm{df} = 2) = 3.03$, $p = 0.22$]. A chi-square test on sex distributions showed that significantly more males ($n = 23$) were in the CU group as compared to the nCU group [$n = 20$; $\chi^2(\mathrm{df} = 1) = 4.69$, $p = 0.03$].

We also compared schizotypy sub-scale scores to a previous normative sample (17) via calculations of Cohen's d (64) with values of ±0.2/±0.5/±0.8 being indicative of a small/medium/large effect size, respectively. As can be seen from **Table 1**, schizotypy values were largely comparable to normative data, as no large effect sizes were found. A medium effect size was indicated for UnEx, with higher values in the normative sample as compared to the current sample (see **Table 1**).

As can be seen from **Table 2**, the groups (CU, nCU) were comparable in age. However, CU as compared to nCU scored higher on UnEx (as a trend), nicotine, cannabis, and alcohol use severity

Table 1 | Means, SDs, and effect sizes (Cohen's *d*), comparing the values of the normative sample with the current sample.

Questionnaire	Norm values ($N = 508$)		Current sample ($N = 83$)		Cohen's *d*
	Mean	SD	Mean	SD	
O-LIFE: UnEx[a]	9.70	6.70	6.36	4.92	0.52
O-LIFE: CogDis[b]	11.60	5.80	10.61	5.28	0.17

[a] *Unusual experiences.*

[b] *Cognitive disorganization.*

(since nCU were screened for weekly cannabis and cigarette use, the comparisons between nCU and CU were not conducted for these variables).

COGNITIVE FUNCTIONING

Group comparisons

The separate univariate ANOVAs on the outcome measures revealed that CU performed significantly worse in the story-recall task, and slightly worse on the working memory task as compared to nCU (**Table 3**). The results for the remaining outcome variables were not significant (**Table 3**).

Regression analyses

The initial correlation analyses between task performances, schizotypy sub-scale scores, age, and drug measures revealed that neither age nor schizotypy related to cognitive functioning (all p-values >0.10, see **Table 4**). Accordingly, age was not further considered.

Table 2 | Age, schizotypy, and drug use statistics comparing CU and nCU.

Variables	CU[c] ($N=35$)		nCU[d] ($N=48$)		t	p
	Mean	SD	Mean	SD		
Age	22.51	5.63	21.67	3.56	0.84	0.40
UnEx[a]	7.63	6.04	5.44	3.71	1.90	0.06
CogDis[b]	10.46	5.75	10.73	4.97	−0.23	0.82
Cigarettes/week	24.66	28.67	n/a	n/a	n/a	n/a
Joints/week	11.14	12.16	n/a	n/a	n/a	n/a
Nicotine use severity	1.94	1.86	0.08	0.45	5.78	**0.00**
Cannabis use severity	2.97	1.95	0.00	0.00	9.03	**0.00**
Alcohol use severity	2.29	1.84	1.31	1.42	2.72	**0.01**

[a] *Unusual experiences.*

[b] *Cognitive disorganization.*

[c] *Cannabis users.*

[d] *Cannabis non-users.*

Values were compared between groups (CU, nCU) using independent t-tests (statistical results are shown in this table; t-values, df = 81, p-values). Significant group differences are highlighted in bold, trends in gray.

UnEx and CogDis on the other hand were included as *a priori* predictions were formulated based on the published literature (see Introduction and Data Analysis).

The significant results from the subsequent regression analyses (see Data Analysis for further details) can be seen in **Table 5**. With regard to the control variables, we found that sex predicted verbal short-term memory. *Post hoc* independent t-tests revealed that women were significantly better than men in the story-recall task [women: $66.63 \pm 12.08\%$, men: $m = 58.54 \pm 15.39\%$; $t(81) = 2.65$, $p = 0.01$]. Entering schizotypy in the second step explained no additional variance on top of sex (see **Table 5**). Drug use severity in the third step predicted significant amounts of variance in the outcome measures. Here, higher alcohol use severity predicted lower working memory performance, and higher cannabis use severity predicted reduced verbal short-term memory on top of sex and schizotypy (**Table 5**).

DISCUSSION

We investigated whether pure cannabis use hampers cognitive performance, or whether cognitive attenuation is also, or even better explained by associated licit drug use and psychotic-like features (schizotypy). For this purpose, we tested cognitive functions commonly associated with drug use and schizotypy in CU and nCU. The main findings were that (i) CU as compared to nCU performed worse on story recall and slightly worse on the two-back task, but not on the TMT, (ii) CU scored higher than nCU on positive schizotypy (as a trend), and drug use other than cannabis, (iii) regression analyses showed that enhanced cannabis use predicted decreased verbal short-term memory, whereas enhanced alcohol use predicted reduced working memory performance, (iv) none of the schizotypy sub-scales explained any additional variance in cognitive functioning. The implications of these findings are discussed below.

ROLE OF CANNABIS USE SEVERITY

Our results showed that CU performed worse than nCU on tasks measuring verbal short-term memory (story recall), and higher cannabis use severity was associated with worse performance in this task. Our results also showed that these relatively negative cognitive implications were not associated with individuals' self-reported schizotypy. The observation that worse story recall is

Table 3 | Descriptive and statistical values for the cognitive measures, comparing performance of CU and nCU.

Variables	CU[b] ($N=35$)		nCU[c] ($N=48$)		$F(1,81)$	p	Partial η^2
	Mean	SD	Mean	SD			
Two-back % target correct	86.00	13.49	90.52	8.07	3.62	0.06	0.04
Two-back mean RT	822.57	164.00	821.42	205.92	0.00	0.98	<0.01
TMT[a] index	23.77	13.58	23.56	16.58	0.00	0.95	<0.01
Story-recall % correct	55.90	14.78	67.21	12.19	14.55	<**0.01**	0.15

[a] *Trail making task.*

[b] *Cannabis users.*

[c] *Cannabis non-users.*

Values were compared with univariate ANOVAs, and significant values are highlighted in bold, trends in gray.

associated with cannabis use is in line with previous studies (3, 13, 46). However, story recall (verbal memory) was the only task that was affected by cannabis use, whereas relatively impaired performance on another cognitive task (working memory as assessed with the two-back task) was related to enhanced alcohol use instead. Previous studies have indicated that cannabis use has a negative impact on working memory performance (46, 65) and mental flexibility (3, 66) as well. Our findings suggest that these previous findings on cannabis use were potentially confounded by concomitant non-excessive alcohol use (3, 67).

Despite some evidence that cannabis use is still associated with cognitive impairments after adjusting for alcohol use (68), independent studies (8, 36) report that CU tend to consume higher amounts of other drugs as well. This additional drug use, as frequently not assessed, might lead to misleading conclusions about cannabis effects on cognition. Particularly licit drug use like alcohol seems to be a relevant confounding factor. For instance, whereas in some studies alcohol use is either statistically controlled for (63) or subjects with alcohol abuse are excluded from participating (13, 14), other studies do not account for this variable (24, 69, 70, 71). Moreover, alcohol and cannabis are thought to exert comparable effects on cognition, i.e., cognitive attenuation in verbal memory (72–74), cognitive flexibility (75, 76), and working memory (77–79). Future studies should consider (non-excessive) licit drug use as a potential confounding factor when investigating the effects of cannabis use on cognition.

Table 4 | Correlations between potential predictor variables and cognitive measures.

Variables	Two-back task % target correct	Two-back task mean RT	TMT[c] index	Story-recall % correct
Age	−0.06	−0.16	−0.08	−0.03
UnEx[a]	−0.08	0.06	0.08	−0.03
CogDis[b]	0.02	−0.01	−0.04	−0.07
Nicotine use severity	**−0.24***	0.08	0.04	**−0.41*****
Cannabis use severity	**−0.27***	0.14	0.10	**−0.47*****
Alcohol use severity	**−0.29****	**0.40*****	**0.28****	−0.07

[a] *Unusual experiences.*
[b] *Cognitive disorganization.*
[c] *Trail making task.*
**Significant at $p \leq 0.05$.*
***Significant at $p \leq 0.01$.*
****Significant at $p \leq 0.001$.*
Significant values are highlighted in bold.

ROLE OF SCHIZOTYPY

Of additional significance was the observation that schizotypy did not explain variance in most cognitive tasks. We do not think that this finding can be explained by deviant features of our sample, because we replicated many previous observations, i.e., that CU as compared to nCU scored slightly higher on measures of positive schizotypy (24, 27, 28, 41, 42, 44). The observation that schizotypy was not importantly related to cognitive functioning would indicate that the impairments in, e.g., working memory (19, 20), cognitive flexibility (21), and verbal memory (22, 23) may be influenced by individuals' concomitant drug use.

Unfortunately, the above mentioned studies did not report on drug use (19, 21–23, 80), or only screened for substance use history without specifying the substances controlled for (20, 81). It is thus possible that substances (e.g., illicit as well as licit) influenced the relationship between schizotypal symptoms and the cognitive functions assessed in these experiments (38–40). In particular, our results suggest that cannabis may be more relevant than schizotypy for cognitive attenuations in verbal short-term memory, and alcohol may be more relevant than schizotypy for cognitive attenuations in working memory (82).

The specific cannabis effects on story recall, but not on the two-back or TMT may also suggest that not all cognitive functions are equally sensitive to cannabis-related attenuations. Even though many studies observe CU to show impairments compared to nCU on tasks measuring working memory (46) and mental flexibility (3, 66), this may not always be the case (71, 83). In fact, different

Table 5 | Significant results (including trends in gray) from the regression analyses assessing the effect of sex (step 1), schizotypy (UnEx[a], CogDis[b]; step 2), and drug use severity (nicotine, alcohol, and cannabis; step 3) on cognitive measures.

Outcome variables	Step	Significant predictor	β-value	Total R^2	ΔR^2	F for ΔR^2
Two-back % target correct	3	Alcohol	−0.25*	0.15**	0.14**	4.25**
Two-back mean RT	1	Sex	−0.21[†]	0.04[†]	0.04[†]	3.61[†]
	3	Alcohol	0.39***	0.18**	0.13**	4.03**
Story-recall % correct	1	Sex	0.28**	0.08**	0.08**	7.02**
	3	Cannabis	−0.41**	0.30***	0.21***	7.46***

[†] *$p \leq 0.10$.*
**Significant at $p \leq 0.05$.*
***Significant at $p \leq 0.01$.*
****Significant at $p \leq 0.001$.*
[a] *Unusual experiences.*
[b] *Cognitive disorganization.*

meta-analyses draw inconsistent conclusions about which cognitive functions qualify as cognitive markers, or endophenotypes for pathological changes. Findings are inconsistent in CU and along the schizophrenia spectrum, with some studies pointing to verbal memory impairments in both populations (65, 84–86), some pointing to cognitive flexibility impairments (86, 87), and others reporting consistent working memory impairments in both patients with psychosis and CU (65, 85, 86). Alternatively, higher THC-content of used cannabis may relate to more prominent cognitive attenuations (88). Therefore, future studies should report the type and/or strength of cannabis used to improve reliability of findings.

Admittedly, all these complex functions tap into a variety of cognitive sub-functions. For this reason, to increase reliability of findings across studies and populations, the research community might consider behavioral markers that are less complex in their cognitive demands (89–92). Additionally, the pathophysiology of psychotic disorders is currently unknown, and the disorders are quite heterogeneous in their phenotypic expression. Consequently, we may increase the reliability of findings by accounting for seemingly related as well as unrelated factors potentially influencing the relationship between cannabis, cognition, and psychosis (-risk). For instance, studies could consider different yet potentially equally relevant personality traits such as those tapping on the autism spectrum (93) or the bipolar spectrum (94, 95). Beyond personality, studies could consider genetic predisposition (96), IQ (97), and neurochemical peculiarities such as dopamine receptor availability (98, 99) that may influence the effect cannabis exerts on cognition. Such factors are also relevant for the link between psychosis and drug use, e.g., genetic predisposition (100, 101), IQ (102–104), and neurochemical peculiarities (99). At present, it is impossible to account for all putatively influential variables, and hence additional studies need to be conducted to replicate our and similar findings, be it clinical, experimental, and/or epidemiological studies.

STUDY LIMITATIONS AND FUTURE RESEARCH

In the catchment area of our study, the "binge drinking culture" reflects on the high acceptance for alcohol use (105). Consequently, we refrained from pre-selecting participants according to their alcohol use, as the recruitment of pure CU (rather than polydrug users) turned out to be challenging, and was not facilitated by the modest incentives we could offer. Likewise, controlling for the co-use of nicotine seemed even more unavoidable, because cannabis is mostly used in combination with nicotine (106). Yet, controlling for nicotine could have been relevant, because nicotine itself might counteract the effects of cannabis on cognition (33, 107–109). We therefore suggest that future studies should elucidate the role of nicotine and cannabis more directly.

The gender composition differed between groups, a difference common to studies such as the current one. This gender difference could have also affected the group differences in story recall. Typically, females perform better on verbal short-term memory tasks than males (110), a finding also observed here. Since the nCU group consisted of more females than the CU, this group difference could alternatively explain the worse story recall in CU. However, since cannabis use related to worse story-recall performance on top of sex in the regression analysis, we deem it unlikely that the group differences are solely due to effects associated with the unequal sex distribution. Nevertheless, future studies on drug use and cognition should aim to control for sex differences.

A final, frequently mentioned study limitation is the sample size, also relevant to the conducted analyses. For regression analyses, the guidelines for recommended sample sizes vary, from using $50 + 8\times\ N$ variables (111–113) to 10 participants per predictor variable (114). Obviously, a larger sample size would always be advisable. Yet, our sample size matches sample sizes in other studies reporting on preselected minority samples of (relatively) pure drug users (3). A potential reason could be firstly, that these individuals are either extremely difficult to motivate, or secondly, that pure users of drugs are a rarity, at least in our study region. The difficulty of finding pure CU may also be reflected in population descriptions over the last 30 years; many studies inferred on the influence of cannabis use on cognition and mental health risk without necessarily ensuring that individuals did not also consume other licit and illicit drugs. We thus face the future challenge to disentangle the impact of a specific drug use or synergetic drug uses on cognition and mental health (115–117).

Finally, cognitive attenuations related to cannabis use seem more overt in heavy as compared to moderate or light users (14, 118, 119). A higher frequency of cannabis use in our sample might have exacerbated the reported cognitive attenuations. Though definitions for heavy use may vary (118, 119), the frequency of cannabis use (joints/week) in our sample seems to indicate heavy use according to a previous report on pure CU (63). To note, our data point to a negligible influence of frequency of pure cannabis use (see Materials and Methods).

CONCLUSION

While pure cannabis and alcohol use seem associated with adverse effects on cognition, other risk factors (e.g., nicotine use) might also be relevant. Schizotypy, on the other hand, seems unrelated to cognitive attenuation. Results stress the importance to control for additional substance use (and non-excessive use in particular), whether illicit or licit, when assessing the effect of schizotypal symptoms and/or cannabis use on cognition. Moreover, heterogeneity of cannabis-related attenuations of specific cognitive functions may be avoided by controlling for additional factors potentially influencing the relationship between cannabis, cognition, and psychosis (-risk).

AUTHOR CONTRIBUTIONS

All authors significantly contributed to the conception or design of the work, the analysis, and interpretation of data for the work, as well as revising it critically for important intellectual content. Dr. Daniela A. Herzig was additionally involved in the data acquisition and drafting the first version of the manuscript. All authors approve of the final version of the manuscript, therefore, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Deficits in agency in schizophrenia, and additional deficits in body image, body schema, and internal timing, in passivity symptoms

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Individuals with schizophrenia, particularly those with passivity symptoms, may not feel in control of their actions, believing them to be controlled by external agents. Cognitive operations that contribute to these symptoms may include abnormal processing in agency as well as body representations that deal with body schema and body image. However, these operations in schizophrenia are not fully understood, and the questions of general versus specific deficits in individuals with different symptom profiles remain unanswered. Using the projected-hand illusion (a digital video version of the rubber-hand illusion) with *synchronous* and *asynchronous* stroking (500 ms delay), and a hand laterality judgment task, we assessed sense of agency, body image, and body schema in 53 people with clinically stable schizophrenia (with a current, past, and no history of passivity symptoms) and 48 healthy controls. The results revealed a stable trait in schizophrenia with no difference between clinical subgroups (sense of agency) and some quantitative (specific) differences depending on the passivity symptom profile (body image and body schema). Specifically, a reduced sense of self-agency was a common feature of all clinical subgroups. However, subgroup comparisons showed that individuals with passivity symptoms (both current and past) had significantly greater deficits on tasks assessing body image and body schema, relative to the other groups. In addition, patients with current passivity symptoms failed to demonstrate the normal reduction in body illusion typically seen with a 500 ms delay in visual feedback (*asynchronous* condition), suggesting internal timing problems. Altogether, the results underscore self-abnormalities in schizophrenia, provide evidence for both trait abnormalities and state changes specific to passivity symptoms, and point to a role for internal timing deficits as a mechanistic explanation for external cues becoming a possible source of self-body input.

Keywords: schizophrenia, passivity symptoms, first-rank symptoms, rubber-hand illusion, hand laterality, agency, body schema, body image

INTRODUCTION

In the field of cognitive neuroscience, the "sense of self" refers to a complex framework, which is derived from cognitive, sensory, and motor systems. In this context, a subjective experience of "self" is drawn, at least in part, from information gained from body and motor senses. Self-abnormalities in schizophrenia have long been documented in the clinical literature. Kurt Schneider noted that symptoms described "a loss of the very contours of the self" (1), and Bleuler (2) described the tearing apart or splitting of psychic functions. Such self-abnormalities appear to be characteristic of schizophrenia (3, 4), and are particularly pronounced in passivity symptoms (experience of alien control), where individuals do not feel in control of their movements and believe that their actions and intentions are controlled by an external agent. In passivity symptoms, the primary experience is that of a perceptual change regarding how the self is experienced alongside the subjective experience of an external locus of control for internally generated events.

A contemporary model suggests that such abnormalities arise from a failure in the mental operations responsible for predicting the sensory consequences of intended motor commands (the forward model), where the brain "anticipates" an action taking place (5–7). Cognitive self-monitoring models, by contrast, have explained the observed self-distortions as a failure of higher order cognitive processes involving source-monitoring, biases, and *post hoc* inferences that enable coherent self-referencing over time (8, 9). It is becoming clear, however, that these proposals are not adequate or sufficient as theoretical frameworks

for motor passivity symptoms (10, 11). Criticisms include that motor commands are neither necessary nor sufficient to engender a sense of agency, and that *post hoc* inferences and biases cannot fully account for pervasive changes in self-experience and self-awareness reported by people with schizophrenia. In support, structured clinical interviews using a clinical–phenomenological approach demonstrate fundamental changes in embodied self-presence, self-experience, and self-judgment in individuals with schizophrenia (12) and in those at high risk of psychosis (13). In addition, disruptions in the forward model should precipitate gross motor problems in people with schizophrenia, for which there is contrary evidence (14, 15).

BODY REPRESENTATION DISTORTIONS AS AN ALTERNATIVE FRAMEWORK FOR EXPLAINING SELF-ABNORMALITIES IN SCHIZOPHRENIA

A focus on purely motor or cognitive mechanisms fails to consider other somatic and psychological processes that are necessary prerequisites for a coherent sense of self. It was recently suggested that self-deficits in schizophrenia may be better described as broad deficits in body representations that extend beyond self-agency (16). This proposal was drawn from evidence showing that the self emerges from the concurrent activation of multiple body representations, which are derived from multimodal sensory input as well as motor monitoring sources, and that are based on anatomical and neural networks, which play a critical role in one's sense of self. Body representations are intrinsically linked to one's sense of awareness, identity, self-concept, and sense of uniqueness. They are needed for the differentiation of body parts and for the accurate performance of purposeful actions.

A general framework for conceptualizing body representations includes at least two important representations: body image and body schema. *Body image* refers to a top-down cognitive representation that integrates the conscious perceptual experiences of one's body and contributes to one's belief and attitude about one's body (17–21). *Body schema* is typically defined as an unconscious dynamic sensory representation that reflects the position and movement of the body and limbs in space (17–20). The validity of these body representations is supported by studies of neurological patients, where localized lesions can selectively impair one or more representations (22–26), and from brain imaging studies pointing to differential activation of neural networks on tasks selective for each body representation (27–31). Finally, for the purposes of the current study, the *sense of agency* is defined as the experience that one is the initiator and in control of one's actions. The sense of agency is different from body representations as it is critically dependent on actions and intentions (32–34).

BODY REPRESENTATION DISTORTIONS IN PEOPLE WITH SCHIZOPHRENIA

As detailed previously, people with schizophrenia have difficulty in correctly attributing agency to self-made movements (35, 36), indicating distortions in agency. There is also emerging evidence for disturbances of these multiple body representations in schizophrenia. For example, empirical findings point to difficulties in imagining movements (37) pointing to deficits in body schema. People with schizophrenia also have abnormal body image, as assessed using a body distortion questionnaire (38). From these findings, it would appear that the internal modeling of the self is weakened or more malleable in people with schizophrenia.

The question of general versus specific deficits in individuals with different symptom profiles, however, has not yet been addressed. Specifically, are these body representation-deficits present in all individuals with schizophrenia or only those with passivity symptoms? According to the philosophical–theoretical tradition of self-disturbances in schizophrenia (3), passivity symptoms represent the more severe and elaborated form of self-disturbances in a continuum from non-psychotic experiences through intermediate phenomena into the manifest psychotic symptoms. Individuals then transit back and forth between manifest psychosis and the intermediary forms as their clinical condition changes over time. According to this view, there should be quantitative differences between people with passivity symptoms compared to individuals with a history of these symptoms and individuals with no lifetime history of passivity. The performance of individuals with schizophrenia with different symptom profile was therefore of interest in the current study.

ASSESSING BODY REPRESENTATIONS IN THE CURRENT STUDY

Body illusions, such as the rubber-hand illusion, are frequently used to examine processes underlying self-recognition. In the rubber-hand illusion, participants watch a fake hand being stroked, while their own hand is synchronously stroked out of view. This produces an illusory sensation of ownership of the rubber hand and a shift in perceived hand location toward the fake hand. A key requirement of the illusion is that of synchronous input between sensory modalities (tactile and vision). In the asynchronous condition, the illusion can be abolished or diminished by introducing a temporal delay between brush strokes and visual feedback (39). This condition allows an examination of the effects of a timing delay on each type of body representation.

People with schizophrenia tend to experience the rubber-hand illusion more strongly (40, 41) and faster (42) compared to healthy controls. Additionally, the relocation of the perceived position of one's own hand toward the image ("proprioceptive drift") has been shown to be greater in schizophrenia than controls, indicating stronger visual capture of proprioceptive information (40). The *projected*-hand illusion, however, has not yet been reported in the schizophrenia literature. The projected-hand illusion uses a live video image of the participant's own hand projected onto a video screen, allowing a more realistic image of the hand than the traditional "rubber-hand" methodology, more precise control over the timing of brush strokes, as well as enhanced merging of reality into the illusion.

This task assesses two aspects of the sense of self in one experimental set-up. Using a post-performance questionnaire, body image can be assessed on domains of "embodiment (of the 'other' projected hand)" and "disembodiment (of one's own hand)," and the sense of agency with the subjective sensation of motor control (over both the "other" and own hand). Psychometric studies show that illusory sensations over the "other" hand are simultaneously associated with a reduction of the same sensations in the real hand (43). For example, embodiment of the "other" hand is proportionally related to disembodiment of

one's real hand, with the total embodiment of both being equal to one single hand (44, 45). A similar balance also exists with the sense of agency (46). Disembodiment (of limbs) and reduced agency (over actions) are clinical features of persons with passivity symptoms, so performance on such measures are of particular interest.

In order to assess the third type of body representation (body schema), the current study employed the hand laterality task (47). In this task, participants are asked to make a judgment regarding whether an image of a hand is that of a right or left hand by mentally rotating their own hand to match the hand on the screen. Both response times and accuracy are recorded. Evidence that imagined movements are dependent upon the body schema and include findings that performance on this task is influenced by the same biophysical constraints that underlie performed actions (48). A recent study shows that schizophrenia individuals ($n = 13$) were impaired on the task (49), although an analysis of passivity symptoms was not conducted.

AIMS AND HYPOTHESES

In the current study, we studied body representations in 53 individuals with schizophrenia and 48 healthy controls on the validated projected-hand illusion (50, 51) and the hand laterality task (47). Individuals with schizophrenia were clustered into subgroups based upon their lifetime history of passivity symptoms. The research questions were as follows: (1) what is the pattern of performance on measures of body schema, body image, and the sense of agency in individuals with schizophrenia compared to controls?; (2) does the evidence point to a stable trait for schizophrenia (no difference between clinical subgroups) or to quantitative differences depending on the passivity symptom profile? Our hypotheses are that body representation distortions will be present in varying degrees in the clinical population: individuals who are currently symptomatic (with passivity symptoms) will have the most severe abnormalities on all body representations, and those with a past history of symptoms, by virtue of their trait vulnerability, will have greater abnormalities than those with no history of symptoms and healthy controls but less than those who are currently symptomatic.

MATERIALS AND METHODS

PARTICIPANTS

The patient sample included individuals with schizophrenia or schizoaffective disorder (53 total, 36 males) recruited from the research database of the WA Family Study of Schizophrenia (52, 53). All patients met both ICD-10 and DSM-IV criteria for a lifetime diagnosis of schizophrenia or schizoaffective disorder, and were community outpatients not currently admitted into a psychiatric hospital and were treated with psychotropic medication. Exclusion criteria included comorbid organic brain disease or substance-use disorder that could account for the psychotic symptoms or language difficulties.

Healthy controls (48 total, 24 males) were recruited through community advertising. Potential controls were excluded if they had a history of a psychotic disorder, or if any of their first-degree relatives had been diagnosed with schizophrenia, schizophrenia-spectrum, or bipolar affective disorder.

The study protocol was explained to all participants and written informed consent was obtained. The study was approved by the North Metropolitan Mental Health Service Human Research Ethics Committee and conformed to the appropriate regulatory standards.

CLINICAL EVALUATION

Clinical evaluation was conducted with the Scales for the Assessment of Positive and Negative Symptoms [SAPS and SANS; (54, 55)]. Passivity symptoms were assessed using the Passivity Symptoms Interview (PSI) (56) with selected items from the Schedule for Clinical Assessment in Neuropsychiatry [SCAN, Version 2.1; items: 17.008, 18.005–18.010, 18.012–18.017, see Ref. (57)]. All symptoms were rated in accordance with stringent definitions and criteria assessed for lifetime history and presence in the last 4 weeks as determined by self-reports and case-note reviews. Patients were rated as having current passivity symptoms (current group) if they reported two or more such symptoms in the past 4 weeks ($n = 20$). Patients were rated as "Past" ($n = 12$) if they had a positive rating of at least two passivity symptoms in the past but not within the past 4 weeks or "Never" ($n = 21$) if they had never experienced these symptoms during any period. Independent classification of patients into groups was conducted by two of the investigators (Kyran T. Graham and Flavie Waters) and rated based on consensus.

EXPERIMENTAL TASKS

Hand illusion

Each participant sat in front of a table with a Fujitsu 17″ color monitor embedded horizontally in the top, with both hands resting on top of the table. The right hand was hidden behind a removable curtain. An image of this hand was captured by an analog camera (AVC-561, AVTECH, Taiwan) and transmitted to the monitor via an analog delay line (DL1B-5379, Ovation Systems Ltd., UK). The real hand and the image of the hand were separated by 15 cm. A photograph of the set-up used can be seen in **Figure 1**. There were two delay conditions in the illusion; *synchronous* (<10 ms video feedback) and *asynchronous* (an additional imposed 500 ms delay). Participant were exposed to each condition once (3 min each), with the order of presentation being counter-balanced across participants. A 20-item questionnaire assessing the subjective experience of the illusion was administered after each condition (46); adapted from Ref. (43). Items relating to the component Deafference were not included as the component does not pertain to body representations. Each item was rated on a 7-point Likert scale ranging from −3 (strongly disagree) to +3 (strongly agree). A recent PCA (46) identified that the following components could be extracted from the questionnaire, assessing body image ("Disembodiment of own hand" and "Embodiment of the 'Other' hand"), and the sense of agency ("Agency over the 'Other' hand," and "Loss of agency over own hand") in both *synchronous* and *asynchronous* conditions. **Table 1** shows the 20 items (Embodiment items 1–8, Disembodiment 13–17, Agency 9–10, and Loss of agency 11–12).

Hand laterality task

For each trial, a picture of a hand, palm down, was displayed on a computer screen (47). Participants were instructed to indicate

if the hand was a left or right hand by pressing an appropriate key on a keyboard. Each picture was either a left or right hand and rotated by either 0°, 90° medially, 90° laterally, or 180°. There were six repeats of each hand/rotation combination for a total of 48 trials per participant. The stimuli were presented in a random order. Participants were instructed not to make major movements of their hands or heads while making the judgments. Four practice trials with feedback were given to each participant before commencing the main experiment. The experiment was produced using E-Prime 1.2 software (Psychology Software Tools, Pittsburgh, PA, USA). In order to rule out possible abnormalities in mental rotation, a similar task was conducted in which the letter F was displayed instead of a hand. The letter was either oriented normally or mirrored along the vertical axis. The same number of trials of letter and rotation combinations was used as the hand laterality task. For both tasks, accuracy and response time were recorded.

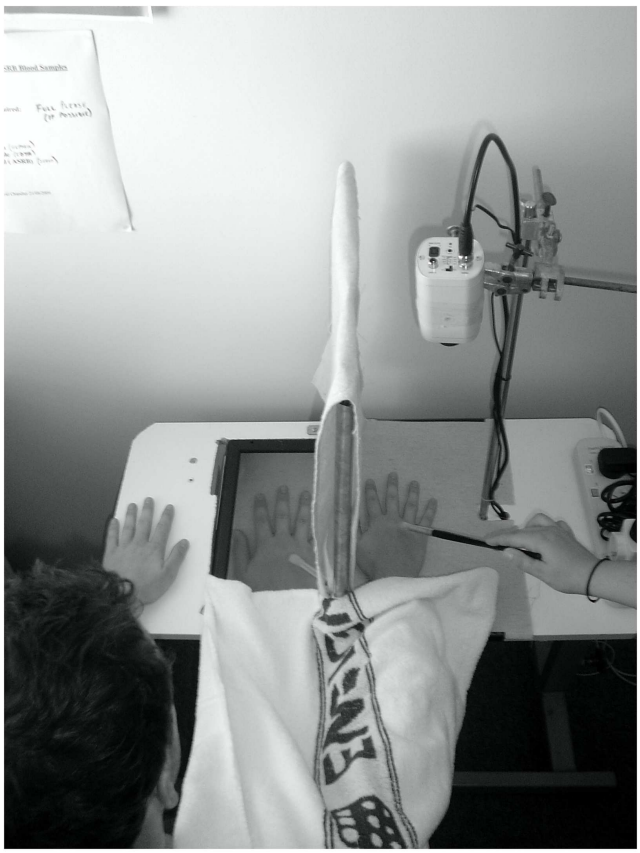

FIGURE 1 | Photograph of the projected-hand illusion is shown.

COGNITIVE TASKS

The Wechsler Test of Adult Reading (WTAR) (58) was included as a measure of pre-morbid intelligence. Trail Making Test Form A (TMTA) (59) provided a measure of speed of processing. The Digit Span (DS) provided a measure of attention span (forward span) and working memory (backward span) (59).

STATISTICAL METHODS

All statistical analyses and figures were completed using the statistical software R [version 3.0.1; Ref. (60)], and the packages "nlme" (61) and "car" (62). Analyses were performed using linear mixed-effects models with the mean score on the relevant subscale as the dependent variable, delay condition (*synchronous* or *asynchronous*) was the within-subjects variable, group (Controls, Current, Past, or Never) as the between-subjects variable and participant as the random effects term. Similarly, for the hand laterality task, separate models were created for (a) mean accuracy (% incorrect) and (b) mean response time (seconds). For these, group was the between-subjects independent variable and rotation (0°, 90° medial, 90° lateral, and 180°) was the within-subjects variable. Performance (% incorrect and response

Table 1 | Questionnaire items used during the projected-hand illusion.

It seemed like . . .	Component
. . . I was looking directly at my own hand, rather than at an image	Embodiment
. . . the image began to resemble my real hand	Embodiment
. . . the image of the hand belonged to me	Embodiment
. . . the image was my hand	Embodiment
. . . the image was part of my body	Embodiment
. . . my hand was in the location where the image was	Embodiment
. . . the image was in the location where my hand was	Embodiment
. . . the touch I felt was caused by the paintbrush touching the image	Embodiment
. . . I could have moved the image of the hand	Agency over the image
. . . like I was in control of the image	Agency over the image
. . . I was unable to move my hand	Loss of agency over own hand
. . . I couldn't have moved my hand if I had wanted	Loss of agency over own hand
. . . I couldn't really tell where my hand was	Disembodiment
. . . my hand had disappeared	Disembodiment
. . . my hand was out of my control	Disembodiment
. . . my hand was moving toward the image	Disembodiment
. . . the image was moving toward my hand	Disembodiment

time) on each rotation for the letter rotation task was included as a covariate in these analyses. Where analysis of deviance (ANODEV) on the terms of the model revealed significant differences, interaction contrasts comparing difference in scores on each of the levels of the factor were performed, i.e., [Controls(Synch) − Controls(Asynch)] − [Current(Synch) − Current (Asynch)]. Alpha was set to 0.05.

RESULTS

PROJECTED-HAND ILLUSION

Demographic information for participants can be seen in **Table 2**. Where there were differences between groups, these data were then entered into the projected-hand illusion analyses as covariates. However, there were no significant effects of any of the covariates for the PHI data ($p > 0.1$) and so these were removed from the final model.

Schizophrenia groups combined

Performance was first examined with a comparison of people with schizophrenia as a group versus healthy controls to determine overall effects of diagnosis while maximizing power to detect an effect. SAPS and SANS scores and chlorpromazine equivalents were included as further covariates in all projected-hand illusion analyses but were removed from the final model, as none were significant. People with schizophrenia reported increased feelings of disembodiment [$F(1, 99) = 29.5$, $p < 0.0001$], and a greater loss of agency over their own hand [$F(1, 99) = 21.3$, $p < 0.0001$] compared to controls, showing greater deficits identifying the experience of their own body.

There were no main effects of group [$F(1, 99) = 1.83$, $p = 0.18$] or interaction [$F(1, 1498) = 2.65$, $p = 0.10$] on the embodiment of the "other" hand component [$F(1, 97) = 3.63$, $p = 0.06$]. Further, there was no significant difference between groups in the sense of agency over the "other" hand [$F(1, 99) = 0.19$, $p = 0.66$].

Group comparisons – body image (embodiment of image)

Analysis of deviance revealed no main effects of group on Embodiment [$F(3, 97) = 0.83$, $p = 0.48$], but there was a significant main effect of delay [$F(1, 1496) = 57.8$, $p < 0.0001$], with ratings being higher in the *synchronous* condition. There was a significant interaction between group (Controls, Current, Past, and Never) and delay condition [$F(3, 1496) = 4.94$, $p = 0.002$]. Interaction contrasts revealed significant differences between Current and each of the other groups: Controls ($p = 0.001$), Never ($p = 0.04$), and Past ($p = 0.0006$). Controls and patients in the Past and Never groups demonstrated embodiment of the hand in the *synchronous* condition, which was reduced in the *asynchronous* condition. By contrast, patients in the Current group showed no difference in performance between the *synchronous* and the *asynchronous* conditions, exhibiting embodiment in both conditions (see **Figure 2A**).

Group comparisons – body image (disembodiment of own hand)

For disembodiment (**Figure 2B**), there was a main effect of group [$F(3, 97) = 13.1$, $p < 0.0001$], but not delay condition [$F(1, 892) = 1.25$, $p = 0.26$] and the interaction was not significant [$F(3, 892) = 6.78$, $p = 0.08$]. Disembodiment of own hand was significantly higher in the Past ($p < 0.0001$), Current ($p < 0.0001$), and the Never groups ($p = 0.01$), relative to controls. The Current and Past groups were marginally significantly different from each other ($p = 0.05$) but both reported higher disembodiment than the Never group (Past $p = 0.009$, Current $p = 0.04$).

Group comparisons – agency (agency over the image)

Analysis of deviance revealed no main effect of group [$F(3, 97) = 0.16$, $p = 0.92$], but there was a significant main effect of delay condition [$F(1, 292) = 19.2$, $p < 0.0001$], with an overall increase in reported agency over the "other" hand in the *synchronous* compared to *asynchronous* condition. The interaction between group and delay condition neared, but did not reach, significance [$F(3, 292) = 7.59$, $p = 0.055$]. However, given the p-value, it was decided that it was reasonable to perform interaction contrasts. **Figure 2C** shows that Controls, Never, and Past all demonstrated increased agency over the "other" hand,

Table 2 | Demographic information of participants.

	Controls ($n = 48$)	Never ($n = 21$)	Past ($n = 12$)	Current ($n = 20$)
Sex (M/F)[a]	24/24	14/7	10/2	12/8
Age (years)[b]	46.2 ± 1.68	42.5 ± 1.57	43.6 ± 2.84	44.0 ± 2.06
Years of education[b]	13.7 ± 0.35	12.9 ± 0.37	13.0 ± 0.54	13.7 ± 0.57
WTAR[b]	104 ± 1.9	100 ± 3.3	95 ± 3.4	96 ± 3.2*
Trail Making Test A[b]	31.9 ± 2.82	53.0 ± 7.47***	51.2 ± 11.5***	45.7 ± 8.68**
SAPS composite[b]	–	12.0 ± 2.3^^^	19.2 ± 3.5	29.2 ± 3.2
SANS composite[b]	–	21.8 ± 3.6	29.8 ± 4.7	24.7 ± 2.5
Chlorpromazine equivalents (mg)[b]	–	677 ± 121	805 ± 140	754 ± 106

Mean ± SEM of selected covariates.

[a] Fisher's Exact Test.

[b] One-way ANOVA with Tukey's HSD post hoc comparisons (Bonferroni corrected).

*Different from controls: *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.*

Different from Pass. Current: ^$p < 0.05$, ^^$p < 0.01$, ^^^$p < 0.001$.

Antipsychotic doses converted into chlorpromazine equivalents using the formulae given in (69–71).

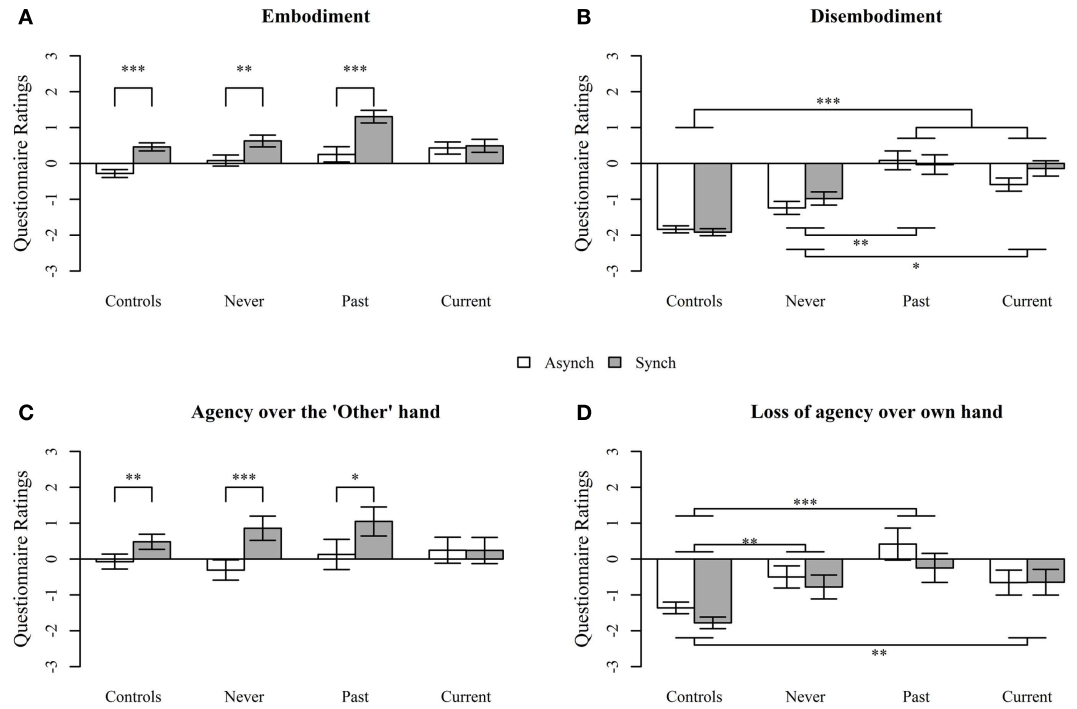

FIGURE 2 | Questionnaire responses assessing (A) Embodiment, (B) Disembodiment, (C) Agency over the "Other" hand, and (D) Loss of agency over own hand, during the projected-hand illusion after asynchronous (Asynch) and synchronous (Synch) stimulation in controls, people with schizophrenia with no history of passivity symptoms (Never), people with a past history of passivity symptoms (Past), and people with current experiences of passivity symptoms (Current). Questions were answered on a 7-point Likert scale. Data are mean ± SEM. $*p < 0.05$, $**p < 0.001$, $***p < 0.0001$.

after *synchronous* compared to *asynchronous* stimulation (treatment contrasts; $p = 0.007$, $p = 0.002$, $p = 0.02$, respectively), while the Current group failed to demonstrate the expected decrease in the *asynchronous* condition ($p = 0.98$) and reported similar levels of agency after both *synchronous* and *asynchronous* stimulation. However, the only pairwise interaction treatment contrast that was significant was between Current and Never groups ($p = 0.009$).

Group comparisons – agency (loss of agency of own hand)

For the loss of agency of own hand component, there was a significant main effect of group [$F(3, 97) = 25.0$, $p < 0.0001$] and a significant effect of delay condition [$F(1, 293) = 3.97$, $p = 0.046$] such that loss of agency ratings were higher in the *synchronous* condition but no significant interaction [$F(3, 293) = 0.49$, $p = 0.69$]. Controls reported significantly less loss of agency over their own hand relative to the Current ($p = 0.004$), Past ($p < 0.0001$), and Never groups ($p = 0.003$), but there were no significant differences between schizophrenia groups (all $p > 0.1$; see **Figure 2D**).

HAND LATERALITY TASK

Scales for the Assessment of Positive Symptoms score, Scales for the Assessment of Negative Symptoms score, and chlorpromazine equivalents were initially included as covariates in all hand laterality analyses, but none had a significant association so they were excluded from the final model.

Schizophrenia groups combined (hand laterality task – response time)

As expected, on response time with the schizophrenia groups and healthy controls, the ANODEV displayed a significant main effect of rotation [$F(3, 700) = 460$, $p < 0.0001$] with the response time on 0° trials significantly different from 90° Medial ($p < 0.0001$), 90° Lateral ($p < 0.0001$), and 180° trials ($p < 0.0001$). There was a main effect whereby individuals with schizophrenia had longer response times across all rotations [$F(1, 99) = 17.7$, $p < 0.0001$], as well as an interaction of group and rotation [$F(3, 693) = 12.8$, $p = 0.005$], indicating a further increase in response time on the 90° lateral ($p < 0.0001$) and 180° rotations ($p < 0.0001$) compared to controls.

Schizophrenia groups combined (hand laterality task – accuracy)

There were significant positive associations between accuracy on the hand laterality task and WTAR scores [$F(1, 78) = 15.9$, $p < 0.0001$, slope = 0.26], and accuracy on the letter rotation task [$F(1, 560) = 4.91$, $p < 0.03$, slope = 0.06], so these variables were retained as covariates. There was a significant effect of rotation [$F(3, 560) = 46.2$, $p < 0.0001$]. Contrasts demonstrated that accuracy on 0° trials is not different to 90° Medial ($p = 0.53$) or 90° Lateral ($p = 0.08$) trials, but significantly different from 180° trials ($p < 0.0001$). There was no significant main effect of group (schizophrenia group versus Controls) in accuracy [$F(1, 78) = 0.14$, $p = 0.71$]. There was a significant interaction between group and rotation [$F(3, 560) = 9.13$, $p = 0.03$] due to the schizophrenia

group being significantly less accurate on the 90° Lateral rotation ($p = 0.03$).

Group comparisons (hand laterality task – response times)

Response time on the letter rotation task covaried significantly with the response time on the hand rotation task [$F(1, 687) = 13.9$, $p = 0.0002$, slope = 0.10]. However, all significant effects remained so with inclusion of the covariate. No other covariates, including chlorpromazine equivalents, were significant. There was a significant main effect of group on response times [$F(3, 97) = 20.6$, $p < 0.0001$]. There was also a significant interaction between group and rotation type [$F(9, 687) = 20.9$, $p = 0.01$]; response times of Current and Past were significantly longer than controls at 90° lateral ($p = 0.03$ and $p = 0.03$) and 180° rotations ($p = 0.009$ and $p = 0.005$), and Never had significantly greater response times compared to Controls at all rotations (0°, $p = 0.01$; 90° medial, $p = 0.002$; 90° lateral, $p < 0.0001$; 180°, $p < 0.0001$) (**Figure 3**).

Group comparisons (hand laterality task – accuracy)

There was a significant interaction between group and rotation [$F(9, 554) = 27.9$, $p = 0.001$], as well as a significant main effect of rotation [$F(3, 554) = 47.4$, $p < 0.0001$]. To investigate the cause of the interaction between group and rotation type, interaction treatment contrasts were performed. There were no significant group differences at 90° medial rotation (all $p > 0.3$). At 90° lateral rotations, the Current and Past (but not Never) were significantly less accurate than controls ($p = 0.006$ and 0.007, respectively). At 180° rotations, only Past were significantly less accurate than controls at 180° rotations ($p = 0.0007$). There was no main effect of group [$F(3, 76) = 0.94$, $p = 0.20$] on accuracy. In regards to the covariates, higher accuracy on the letter rotation task was associated with higher accuracy of hand laterality judgments [$F(1, 554) = 4.61$, $p = 0.01$, slope = 0.06], and a higher WTAR score was associated with higher accuracy [$F(1, 76) = 14.9$, $p = 0.002$, slope = 0.26]. All significant effects remained after inclusion of the covariates.

DISCUSSION

The main aim of the current study was to assess the integrity of body representations in individuals with schizophrenia compared to controls and the pattern of performance with regards to the presence of passivity symptoms on a body illusion and a hand laterality task.

WHAT IS THE PATTERN OF PERFORMANCE IN INDIVIDUALS WITH SCHIZOPHRENIA COMPARED TO CONTROLS?

Individuals with schizophrenia showed abnormal performance on both the hand illusion and hand laterality tasks. During the hand illusion, individuals with schizophrenia, as a group, showed increased disembodiment of their own hand, as well as a decreased sense of agency over their own hand, relative to controls.

The hand illusion, with its subjective reports, provides a particularly convenient method to examine components of body representations and self- and non-self-dimensions in one experimental set-up. The current study showed dissociation in performance by people with schizophrenia between *self*-embodiment/agency and *other*-embodiment/agency. Specifically, there was no significant difference between the schizophrenia and controls groups on embodiment and sense of agency over the "other" hand, although the clinical group was particularly impaired on trials requiring the processing of their own (self) body. This perhaps suggests that the representation of other/external people is relatively preserved in schizophrenia, but that the representation of their own body is impaired. In other words, these individuals may be particularly susceptible to disruptions in self-processes, producing a sense of disconnectedness from their own body, but that the embodiment and sense of agency over external objects/bodies are unaffected.

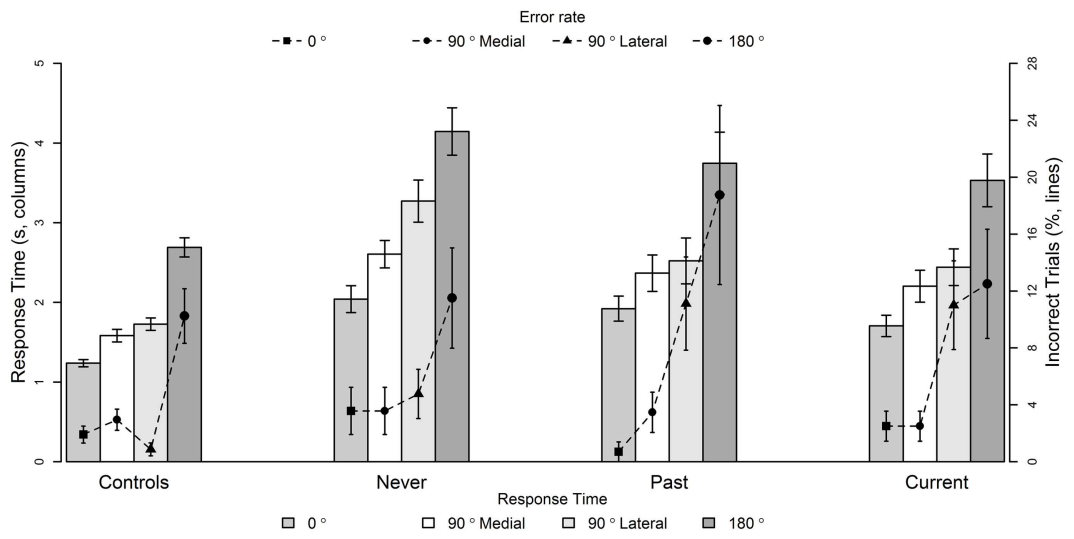

FIGURE 3 | Mean response times (seconds, columns) and inaccuracy (%, lines) of hand laterality judgments at 0°, 90° Medial, 90° Lateral, and 180° rotations for Controls, people with no history of passivity symptoms (Never), people with a past history of passivity symptoms (Past), and people with current experiences of passivity symptoms (Current). Data are mean ± SEM. See text for treatment contrasts.

In a speculative tone, the imbalance between self- and non-self-representations may give rise to distortions regarding the inference of other people's intention, perhaps triggering or increasing the vulnerability to delusions.

Disordered self-agency is a common finding in experimental tasks testing the forward model and cognitive self-monitoring models (36, 63–66). However, few studies have demonstrated disembodiment in schizophrenia. While patients frequently complain of diminished representations of the bodily self (1, 4), depersonalization and feeling of disembodiment (67, 68), and self-referential processing difficulties (66, 67), such subjective reports are rarely assessed in experimental conditions. Altogether, the current findings, using a hand illusion, provide support for anomalies in self-agency and self-ownership in this group.

Performance on the hand laterality task provided evidence of additional changes in body schema. On this task, individuals with schizophrenia took significantly longer to respond than controls. In addition, this clinical group had significantly lower accuracy on 90° lateral and 180° rotation trials. These are the most difficult trials, even in healthy groups, and performance is typically less accurate and slower than on the other trials (47). In individuals with schizophrenia, this pattern of performance on error and latency measures could not be explained simply in terms of impaired visuospatial abilities or generally slower responses, since controlling for performance on the letter rotation task with the same rotation conditions did not change the results. Given that the hand laterality task is under the same biophysical constraints as performed actions, the current results point to specific difficulties in the processes involving the synchronization of proprioceptive and tactile inputs into a representation of the body in space in schizophrenia. These findings on the hand laterality task underscore those of de Vignemont et al. ($n = 13$) (49). In contrast to the current study, however, they showed an increase in errors on all rotations in their schizophrenia group relative to controls. Their task was similar to ours, so it is likely that differences in patient characteristics or in statistical power contributed to this small difference in performance.

Together, the current findings point to deficits in sense of agency, body image, and body schema in schizophrenia. Performance on these tasks was not related to chlorpromazine equivalents, so antipsychotics dosages are an unlikely contributor to performance. Similarly, performance on the task was not correlated with other clinical or cognitive performance score. We believe that it is the first report of deficits in multiple body representations in schizophrenia.

DOES THE EVIDENCE POINT TO A STABLE TRAIT FOR SCHIZOPHRENIA (NO DIFFERENCE BETWEEN CLINICAL SUBGROUPS) OR TO QUANTITATIVE DIFFERENCES DEPENDING ON THE PASSIVITY SYMPTOM PROFILE?

If abnormal body representations represent a stable trait for schizophrenia *in toto,* then no significant differences among Current (current presence of passivity), Past (past history of passivity), and Never (no history of passivity) would be expected, although they would still perform differently from controls. Only partial evidence was found for this suggestion. Specifically, evidence for such a "stable trait" was only observed in the domain of agency, where a reduced sense of agency over one's own hand was a common feature of all three patient groups.

By contrast, performance on the other variables supported our initial hypothesis that there should be quantitative differences between people with passivity symptoms ("Current") compared to individuals with a history of these symptoms ("Past"), and individuals with no lifetime history of passivity ("Never"). Performance on tasks assessing body image suggested quantitative differences depending on the passivity symptom profile of the clinical group. Individuals with passivity symptoms (both current and past) had significantly greater changes in body image as indicated by their higher rating of items relating to disembodiment compared to the group with no history of these symptoms, who in turn reported more disembodiment compared to healthy controls.

In accordance with the above, on the hand laterality task, the Current and Past groups demonstrated reduced accuracy on judgments of the 90° lateral and 180°(Past only) rotations. This finding is in line with demonstrations of impaired performance on a task of motor imagery in people with motor passivity symptoms (37). While this points to problems in body schema, it is important to note that actions and proprioception remain largely unimpaired in this group (14, 15). This suggests that only some subcomponents of body schema are impaired, either in the access pathways to this information or in the integration with other body representations (37).

In sum, the evidence points to both general (trait) deficits in all individuals with schizophrenia (the sense of agency) and quantitative (specific) differences depending on the passivity symptom profile (body image and body schema). Questions remain, however, regarding the processes that separate individuals with current passivity symptoms from those with a history of these symptoms. Both groups show deficits in sense of agency, body image, and body schema, so these processes are not sufficient alone for passivity symptoms. What determines whether patients experience these symptoms? A clue lies in the examination of performance on the hand illusion, specifically on the asynchronous condition.

DECREASED SENSITIVITY TO TIMING DELAYS ASSOCIATED WITH PASSIVITY SYMPTOMS

On all measures of the hand illusion involving timing delays, individuals in the Current passivity group distinguished themselves from the other groups. Most remarkably, they failed to demonstrate the normal reduction in the body illusion typically seen with a 500 ms delay in visual feedback (*asynchronous* condition). This performance was specific to those in the Current group, as the other clinical groups (including the Past group) showed the expected illusory decrease on the *asynchronous* condition. In other words, individuals with passivity symptoms continued to experience illusions of embodiment and sense of agency over the "other" hand, when the other groups did not. This suggests that the temporal window that provides links between self and external stimuli is significantly, and abnormally, elongated in people with passivity symptoms. Alternatively, it is possible that the Current group uses temporal cues during multisensory integration to a lesser extent than the other groups.

The functional significance of this finding cannot be understated, given that internal timing precision is critical for a range of processes including sensory–motor awareness and self-recognition (66, 72, 73). Precise timing is needed for the synchronization of motor, cognitive, and sensory signals. It is also needed to shape sensory awareness and in the formation of causal mental associations. Specifically, voluntary actions, which are followed by a sensory event, are perceived as shifted closer together in time than they actually are, a psychological phenomenon termed intentional binding (74), which contributes toward the sense of self-agency. Abnormal internal timing mechanisms in people with passivity symptom therefore have much explanatory power for their disordered self-attribution system. Other evidence is provided by studies showing time perception impairments in individuals with schizophrenia (75, 76). Passivity symptoms studies also show dysfunctions in cognitive and motor timing. Specifically, these individuals perceive external events to be closer in time together than they are (66, 77, 78), which may impact on the integrity of self- and non-self-attribution processes.

The current hand illusion findings are particularly pertinent, because they show that individual with passivity symptoms experiences an illusory sensation of ownership and agency over an image that is spatially and temporally disjointed from the sensorimotor processes linked to their real hand. It is therefore not surprising that these individuals do not feel in control of their movements, and that they experience confusion regarding the origins of their actions and intentions. Such fragmented phenomena would lead to substantial confusion for internally generated events. If a larger window of integration was indeed closely associated with passivity symptoms, it would be expected to have impact on other behaviors and also other non-body-related illusions such as the ventriloquist illusion.

A possible mechanism might occur via dopaminergic pathways. Using an amphetamine challenge in healthy volunteers as a model of psychoses-related responses in the rubber-hand illusion, our group (44) found that amphetamine appeared to increase the temporal envelope of associability of the rubber-hand visual cues to the feel of the stroking (i.e., had a selective effect of increasing the illusion in the *asynchronous* condition) in a profile of performance, which was similar to the pattern of performance in the Current group. Together with their functional role of assigning salience to external stimuli (35), dopaminergic pathways may well contribute to confusion, and misattribution, of agency via changes in the normal temporal window for associability such that external cues become a possible source of body input.

STRENGTHS AND LIMITATIONS OF THE CURRENT STUDY

It should be noted here that the hand illusion offers significant advantage over other paradigms assessing sense of agency in schizophrenia (35, 36). Notably, subjective reports of *online and prospective* actions (e.g., "I am able to move it") in the hand illusion are superior to tasks assessing actions *retrospectively* ("I moved it"), therefore overcoming criticisms about the involvement of other cognitive processes (35), which render such retrospective predictions unreliable (36) [also see Ref. (14, 79)]. Such differentiation between prospective and retrospective assessments is thought to be significant when assessing agency reliably (35). That the items of the questionnaire of the current study assessed *prospective* agency possibly explains why there was no significant difference between the schizophrenia groups on the loss of agency over own hand questions; it would appear that the changes in agency are limited to *retrospective* agency in passivity symptoms. Confirmation of this finding could not be carried out as the current study did not assess *retrospective* agency.

A further limitation of the current study is that Current group had a significantly higher level of positive symptoms as assessed on the SAPS. It may therefore be that overall illness severity contributed to the current results, rather than the presence of passivity symptoms. However, several lines of evidence argue against this proposal: (i) there were no significant associations of SAPS scores with any of the dependent variables; (ii) SANS scores did not differ between groups; (iii) chlorpromazine equivalents did not differ between groups; and (iv) the groups did not differ from each other on cognitive performance.

CONCLUSION

To conclude, the current study demonstrated both stable traits in schizophrenia (sense of agency) and some quantitative differences depending on passivity symptom profile (body image and body schema). In addition, the presence of passivity symptoms was linked to an enduring experience of body illusion that was resistant to both spatial separation and temporal delay. Our proposal is that passivity symptoms are linked to deficits in body representations encompassing body image and body schema, changes in the sense of agency, alongside internal timing problems that contribute to excessive associability with external sensory stimuli, producing the sensation that one's actions are controlled by an external agent.

AUTHOR CONTRIBUTIONS

Kyran T. Graham conducted all participant testing, statistical analyses and wrote the first draft of the manuscript. Flavie Waters and Assen Jablenksy contributed to the conception of the project and to the design of the study. Kyran T. Graham, Mathew T. Martin-Iverson, and Nicholas P. Holmes provided input into the experimental procedures and testing. All authors contributed to manuscript drafts.

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Neurophysiological correlates of configural face processing in schizotypy

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Background: Face processing impairment in schizophrenia appears to be underpinned by poor configural (as opposed to feature-based) processing; however, few studies have sought to characterize this impairment electrophysiologically. Given the sensitivity of event-related potentials to antipsychotic medications, and the potential for neurophysiological abnormalities to serve as vulnerability markers for schizophrenia, a handful of studies have investigated early visual P100 and face-selective N170 in "at risk" populations. However, this is the first known neurophysiological investigation of configural face processing in a non-clinical schizotypal sample.

Methods: Using stimuli designed to engage configural processing in face perception (upright and inverted Mooney and photographic faces), P100 and N170 components were recorded in healthy individuals characterized by high ($N = 14$) and low ($N = 14$) schizotypal traits according to the Oxford–Liverpool Inventory of Feelings and Experiences.

Results: High schizotypes showed significantly reduced N170 amplitudes to inverted photographic faces. Typical N170 latency and amplitude inversion effects (delayed and enhanced N170 to inverted relative to upright photographic faces, and enhanced amplitude to upright versus inverted Mooney faces), were demonstrated by low, but not high, schizotypes. No group differences were shown for P100 analyses.

Conclusions: The findings suggest that neurophysiological deficits in processing facial configurations (N170) are apparent in schizotypy, while the early sensory processing (P100) of faces appears intact. This work adds to the mounting evidence for analogous neural processing anomalies at the healthy end of the psychosis continuum.

Keywords: schizotypy, configural processing, face processing, N170, P100

INTRODUCTION

Given the social cognitive anomalies characteristic of schizophrenia, emotion processing has received substantial research attention (1–6). Overwhelmingly, significant impairments in emotion perception are reported (7), and these appear present and stable from pre-onset to chronic multi-episode patients (2). A more recent line of inquiry has suggested that deficient facial emotion processing in schizophrenia may be underpinned by basic visuoperceptual deficits (8, 9), although electrophysiological evidence of this is not always demonstrated. Studies using neutral face stimuli have verified a primary deficit in the processing of configural information (described below), with a relative overreliance on facial feature processing by patients with schizophrenia (10, 11), and in ultra-high risk individuals (12). This appears to extend to non-face processing as well (11, 13), supporting a generalized bias for local relative to global perceptual processing.

In the context of face perception, configural processing refers to (i) the basic detection of the face formation (i.e., eyes above nose above mouth; first-order relations), (ii) the uniting of these as a gestalt or whole image (holistic processing), and (iii) an assessment of the spatial relationships between facial features, thought to underlie identity processing (second-order relations) [see Ref. (14, 15)]. The disruption of configural processing when a face is inverted produces the "face-inversion effect" (FIE) (16): upside-down faces are more difficult to perceive, discriminate, and recognize, demonstrated by a decrease in accuracy and increase in reaction times (RT) compared with upright faces, first reported by Yin (17). The FIE has been researched extensively [e.g., Ref. (14, 16, 18, 19)], and in schizophrenia the effect is often absent, aligned with evidence for a configural processing deficit (20–22), however, see Ref. (23) for evidence of the FIE in patients).

The different stages of face processing are reflected by the P100 and N170 event-related potentials (ERPs). The P100 component is an occipitally distributed positive deflection, with a typical peak latency between 80 and 120 ms, and is associated with early stages of visual information processing (24, 25). The N170 component is maximal over the ventral occipitotemporal cortex with a peak latency between 140 and 200 ms post stimulus onset. N170 amplitude is consistently larger for faces compared to other objects, and for this reason has been considered "face-selective" (26–28). Various attempts have been made to define N170 face-specificity further, for instance, in response to eyes only (26, 29, 30), facial emotion (31–34), and identity encoding (28). One group has even argued controversially against N170 face selectivity (35), however, most evidence points toward an index of face-specific early cortical processing (36–41).

The N170 is also modulated by configural face processing, with effects reported in response to whole faces, but not half faces (42), schematic faces that provide spatial face configuration but no distinguishable featural face information (i.e., first-order configural information) (14, 43) and two-tone Mooney faces (44) that rely on holistic processing (global gestalt) to be perceived (14, 45, 46). Reliable modulation of the N170 component is also demonstrated by the FIE: upside-down faces consistently elicit a delayed latency and enhanced amplitude over usual N170 occipitotemporal electrodes, relative to upright faces (14, 26, 43, 47). This is generally regarded as further evidence of N170 sensitivity to configural face information. Although the N170 effects in response to the inversion of schematic and Mooney faces are less consistent, a delayed and reduced N170 to upside-down schematic faces (14, 48), and reduced N170 amplitude to upside-down Mooney faces (45, 46) have been shown.

Reductions in P100 amplitude to various visual stimuli have been demonstrated in patients with schizophrenia (49–51) as well as in unaffected first-degree relatives (52), those with an "at risk" mental state (53), in schizotypy (54), and in non-pathological healthy individuals prone to visual hallucinations (55). This suggests an association between schizophrenia and impoverished visual input, and is supported by existing patient deficits in attention (56–58), as well as visual scan paths characterized by fewer visual fixations, longer duration of fixations/saccades, and smaller saccade amplitudes (21, 59, 60). However, P100 deficits have not always been reported in patient studies (13, 61–64), or in schizotypy (25). It is also noteworthy that P100 effects have typically been recorded in response to basic visual stimuli (i.e., isolated gray/white check images and line drawings) (50–52, 65, 66), with only a handful of studies demonstrating P100 deficits to (emotional) face stimuli in patients (49, 67), and in those at risk for psychosis (53). Last, antipsychotic agents have known effects on neural activation (68, 69). An increase in P100 latency during visual discrimination has previously been shown following an acute dose of bromazepam (70).

In contrast, N170 studies in schizophrenia, although few, have consistently demonstrated reduced N170 amplitude (34, 49, 63, 67, 71), and delayed N170 latency (49) relative to healthy samples. However, N170 amplitude reductions have only been shown in an at-risk population by one study (53), with no evidence for N170 effects reported in first-degree relatives (34), and in individuals prone to visual hallucinations (55). This is surprising given the hereditary nature and spectrum account of psychosis. Shared neurocognitive deficits are commonplace in healthy yet prone individuals (72–76), and the potential for neural markers to serve as endophenotypes in schizophrenia has been established [e.g., Ref. (77, 78)]. Thus, further evidence is necessary to determine whether face processing deficits illustrated neurophysiologically at N170 in patients are shared by individuals prone to psychosis.

Moreover, with rare exception [i.e., Ref. (55, 79)], the N170 literature has notably used emotional face stimuli (34, 49, 53, 63, 67, 71, 80). Thus, more evidence for the ERP correlates of configural face processing, without the potentially confounding positive and negative valence information, is also necessary. Given the established effect of pharmacological agents on neural activation (68–70), individuals prone to psychosis, and medication naïve, provide an ideal method of investigating analogous neural processing deficits (73, 74, 81–85), without concern for medication, and other potential confounds introduced by clinical samples (i.e., long-term hospitalization, social isolation) (82, 86). With this in mind, schizotypy provides a valuable model of investigation. To our knowledge, the N170 response in schizotypy has not yet been reported.

This study aimed to expand on existing literature by avoiding emotionally laden stimuli and clinical confounds while recording neural markers of face processing. Using stimuli designed to engage configural processing in face perception (upright and inverted Mooney and photographic faces), we sought to determine the ERP correlates (P100, N170 components) of configural face processing in schizotypy. We expected that, in high schizotypes, reduced P100 amplitudes would indicate impoverished visuosensory input, whereas reduced N170 amplitudes would indicate impaired face processing. Anomalous ERP responses to (i) Mooney faces, and (ii) inverted stimuli of both types, would provide evidence of configurally specific face processing deficits.

MATERIALS AND METHODS

PARTICIPANTS

Thirty participants (15 male), between ages 18 and 55 years were recruited from RMIT University, Melbourne and the Mental Health Research Institute (MHRI) participant database. Two (1 male) were excluded from the N170 analyses due to (i) inadequate accepted trials (inverted Mooney stimuli), and (ii) a corrupted data file ($M = 27.24$ years, SD = 7.48, 14 male). A third was removed from the P100 analyses due to poor quality recording on principal electrode OZ ($M = 27.20$ years, SD = 7.62, 14 male). All had normal or corrected to normal visual acuity, IQ within the average range [National Adult Reading Test IQ; NART; (87)], no concurrent alcohol or substance abuse, and no personal or family history of psychopathology (self-report).

Schizotypal personality

The Oxford–Liverpool Inventory of Feelings and Experiences [O-LIFE; (88)] was completed as a measure of psychosis-proneness for each participant. The O-LIFE is a 159 yes/no item self-report questionnaire, which measures four distinct schizotypy

Table 1 | Demographic characteristics of high and low schizotypy.

	Mean (Standard Deviation)			
	P100		N170	
	Low schizotypy ($n = 13$)	High schizotypy ($n = 14$)	Low schizotypy ($n = 14$)	High schizotypy ($n = 14$)
Age	30.16 (9.69)	24.45 (3.54)*	30.03 (9.32)	24.46 (3.54)*
Gender (M/F)	6/7	8/6	6/8	8/6
NART IQ	108.15 (8.65)	104.29 (8.11)$^{\#}$	108.43 (8.37)	104.29 (8.11)†
O-LIFE scales				
Unusual experiences	4.46 (5.36)	7.64 (5.89)	4.14 (5.29)	7.64 (5.89)
Cognitive disorganization	**4.46 (2.30)**	**12.57 (4.27)*****	**4.21 (2.39)**	**12.57 (4.27)*****
Introvertive anhedonia	2.00 (1.29)	5.43 (3.03)***	1.93 (1.27)	5.43 (3.03)***
Impulsive non-conformity	6.31 (2.94)	9.36 (3.30)*	6.14 (2.88)	9.36 (3.30)**

O-LIFE; Oxford–Liverpool Inventory of Feelings and Experiences (88). High and low schizotypy was defined by the Cognitive Disorganization dimension (M[SD] values in bold font).

The significant age difference reflects an outlier (n = 1) in the low schizotypy group (results did not change when this outlier was removed).

****$p < 0.001$; **$p < 0.01$; *$p < 0.05$.*

$^{\#}p = 0.24$ $^{\dagger}p = 0.20$.

dimensions with high internal consistency: unusual experiences ($\alpha = 0.89$), cognitive disorganization ($\alpha = 0.87$), introvertive anhedonia ($\alpha = 0.82$), and impulsive non-conformity ($\alpha = 0.77$) (89). A median split of the O-LIFE Cognitive Disorganization dimension defined high/low schizotypy groups. Cognitive Disorganization includes deficits in attention, concentration, decision making, and social anxiety, and the scale was deemed most appropriate because it assesses traits that reflect these cognitive deficits as well as the positive symptoms of psychosis (88, 90)[1]. Moreover, self-face recognition failures correlate with cognitive perceptual/disorganized schizotypy dimensions (90). Groups were matched on NART IQ (see **Table 1**).

FACE RECOGNITION TASKS

Two computerized tasks (20 min duration) were completed during electroencephalographic (EEG) recording. These were counterbalanced, and stimulus order was randomized for each participant. A short break was given after each 10 min block. Task One stimuli were a series of 40 original Mooney faces (44). These were digitally manipulated and repeated to create four separate conditions: *upright face, inverted face, upright disorganized face*, and *inverted disorganized face*[2]. A total of 640 stimuli were presented, with 160 per condition. Twelve[3] neutral grayscale photographic faces were used as Task Two stimuli [Ekman and Friesen series, (91)]. The same four conditions as in Task One were created, with a total of 576 stimuli presented (144 per condition).

All participants were shown a printed example of each condition type prior to the task. They fixated on central fixation cross with a random duration from between 800 and 1200 ms between stimuli, and were shown the images for 200 ms (stimuli were thus on screen for the duration of the critical time period for both P100 and N170). Using a two-button control, participants indicated when they saw either an intact (left button) or disorganized (right button) face. Accuracy and RTs were recorded. These data were submitted to repeated measures analysis of variance (ANOVA) with task (Mooney and photographic faces) and orientation (upright and inverted) as within-subjects factors, and schizotypy (high and low) as the between subjects factor.

ELECTROPHYSIOLOGICAL ACQUISITION AND DATA PROCESSING

Electroencephalographic activity was recorded continuously from 64 scalp sites (10/20 International system, *Neuroscan 4.2*, amplified using *SynAmps2* system). Recording sites included eight midline electrodes (FPZ, FZ, FCZ, CZ, CPZ, PZ, POZ, OZ), 28 electrodes over each hemisphere (FP1/FP2, AF3/AF4, AF7/AF8, F1/F2, F3/F4, F5/F6, F7/F8, FC1/FC2, FC3/FC4, FC5/FC6, FT7/FT8, C1/C2, C3/C4, C5/C6, T7/T8, CP1/CP2, CP3/CP4, CP5/CP6, TP7/TP8, P1/P2, P3/P4, P5/P6, P7/P8, PO3/PO4, PO5/PO6, PO7/PO8, O1/O2, CB1/CB2), and the left and right mastoids. A nose reference was used during acquisition and an average reference montage was calculated offline. The midline electrode between FPZ and FZ served as the ground. Electrooculogram (EOG) was measured at FP1.

Signals were amplified 20,000× and digitized at a sampling rate of 1000 Hz with a band-pass filter of 0.1–100 Hz (24 dB/octave; zero phase shift). Digital codes were sent from the stimulus-presentation computer, and response button-press, to mark the onset and type of each stimulus, and the participant response, respectively. Movement-contaminated EEG sections were discarded, and continuous data files were corrected for eye-blinks and divided into epochs from 100 ms pre-stimulus to 500 ms post-stimulus. Following baseline correction, epochs with artifacts that exceeded $\pm 100\,\mu V$ were rejected. Only trials with the correct

[1]The remaining three dimensions reflect positive and negative, but not cognitive, symptoms.

[2]The disorganized stimuli were included to provide a task and are not relevant to analyses.

[3]Tasks one and two had an imbalance of original stimuli due to the availability of images from the Ekman and Friesen series (91). The total number presented per condition was matched as closely as possible.

Table 2 | Mean (SD) accepted trials per condition.

	Mooney		Photographic	
	Upright	**Inverted**	**Upright**	**Inverted**
P100 analyses				
Low schizotypy	122.85	73.08	109.46	109.38
	(60.40)	(44.78)	(59.26)	(53.64)
High schizotypy	131.93	80.43	137.86	106.07
	(65.81)	(48.95)	(70.97)	(28.58)
N170 analyses				
Low schizotypy	123.21	75.07	110.64	106.57
	(58.04)	(43.70)	(57.11)	(52.60)
High schizotypy	131.93	80.43	137.86	106.07
	(65.81)	(48.95)	(70.97)	(28.58)

Reduced accepted trials for P100 analyses reflects the removal of a dataset (n = 1) due to poor quality recording on principal electrode OZ.

Table 3 | Mean (SD) accuracy and reaction times per condition.

	Mooney		Photographic	
	Upright	**Inverted**	**Upright**	**Inverted**
% correct				
Low schizotypy	87.2	53.9	96.9	94.7
	(4.7)	(17.7)	(2.8)	(6.0)
High schizotypy	83.8	48.3	97.2	94.4
	(12.6)	(18.9)	(2.6)	(4.7)
RTs (ms)				
Low schizotypy	696.1	809.8	638.2	687.2
	(99.7)	(128.9)	(91.4)	(106.9)
High schizotypy	690.4	791.1	632.5	681.9
	(56.5)	(97.0)	(58.7)	(49.7)

behavioral responses ($N > 20$ p/condition)[4] were included and filtered at 0.5–35 Hz (24 dB/octave; zero phase shift) (**Table 2**). ERPs were created by averaging together stimuli of the same condition subtype.

DATA ANALYSIS

Component P100 was measured as the maximal positive deflection between 80 and 120 ms (25) at electrodes O1, OZ, and O2 [established optimal occipital scalp sites; (25, 51, 53, 67, 70)]. Peak latencies and amplitudes from baseline were submitted to repeated measures ANOVA, with task (Mooney and photographic faces) and orientation (upright and inverted) as within-subjects factors. The N170 was measured as the maximal negative deflection between 140 and 200 ms (14, 28, 45) at PO7 and PO8 (41, 48). Peak N170 latencies and amplitudes from baseline were submitted to repeated measures ANOVA, with task (Mooney and photographic faces), orientation (upright and inverted), and hemisphere (left and right) as within-subjects factors. High and low schizotypy served as the between subject factor for all analyses. The Greenhouse–Geisser epsilon correction factor was applied to account for possible effects of non-sphericity where appropriate. To further investigate amplitude differences at N170, independent sample *t*-tests were run using the mean amplitude across PO7/PO8 components. Relationships between ERP data and O-LIFE scores were investigated by Spearman's correlation coefficients.

RESULTS

BEHAVIORAL DATA

An adequate number of trials remained for all but one participant. Two others had accepted trials in the 20s, and the remainder had >37 (**Table 2**). The accuracy and RT data are presented in **Table 3**. Participants correctly identified a greater number of photographic than Mooney faces; $F(1,26) = 146.77$, $p < 0.001$, $\eta_p^2 = 0.85$ and a greater number of upright than inverted faces; $F(1,26) = 147.77$, $p < 0.001$, $\eta_p^2 = 0.85$. A task × orientation interaction reflected a large decline in accuracy for the inverted Mooney faces, not shown to the inverted photographic faces; $F(1,26) = 124.47$, $p < 0.001$, $\eta_p^2 = 0.85$. These findings were mirrored by RTs: participants responded faster to photographic than Mooney faces; $F(1,26) = 62.68$, $p < 0.001$, $\eta_p^2 = 0.85$ and faster to upright than inverted faces; $F(1,26) = 197.99$, $p < 0.001$, $\eta_p^2 = 0.85$. A task × orientation interaction once again reflected much slower responses to inverted Mooney faces; $F(1,26) = 24.94$, $p < 0.001$, $\eta_p^2 = 0.85$. Neither accuracy nor RT differentiated the schizotypy groups: accuracy, task $p = 0.33$, orientation $p = 0.64$; and RTs, task $p = 0.76$, orientation $p = 0.58$ (**Table 3**).

EVENT-RELATED POTENTIALS

P100

Mean (SD) amplitudes and latencies are presented in **Table 4**, and grand-averaged waveforms are illustrated in **Figure 1**. P100 latency was increased for inverted relative to upright faces at electrode O1; $F(1,25) = 6.22$, $p = 0.02$, $\eta_p^2 = 0.85$. Larger amplitudes were shown to photographic than Mooney faces at all three occipital sites: (i) O1; $F(1,25) = 10.20$, $p = 0.004$, $\eta_p^2 = 0.85$ (ii) OZ; $F(1,25) = 10.81$, $p = 0.003$, $\eta_p^2 = 0.85$ (iii) O2; $F(1,25) = 8.68$, $p = 0.007$, $\eta_p^2 = 0.85$. Greater amplitude to inverted versus upright faces was shown at electrode O2 only; $F(1,25) = 14.74$, $p = 0.001$, $\eta_p^2 = 0.85$ (trend level at OZ, $p = 0.06$). No differences between schizotypal groups were shown for P100 latency: (i) O1; $p = 0.85$, (ii) OZ; $p = 0.54$, (iii) O2; $p = 0.61$, or P100 amplitude: (i) O1; $p = 0.19$, (ii) OZ; $p = 0.63$, (iii) O2; $p = 0.35$. No other significant P100 effects were shown.

N170

Latency. Mean (SD) amplitude and latency to upright and inverted stimuli for both tasks are shown in **Table 5**, and N170 waveforms at P07/08 are shown in **Figure 2**. Earlier N170 latencies were shown to photographic ($M = 154.72$ ms, SD = 10.06), than to Mooney ($M = 174.63$ ms, SD = 10.33) faces: $F(1,26) = 79.52$, $p < 0.001$, $\eta_p^2 = 0.85$ and to upright ($M = 163.02$ ms, SD = 8.68) than inverted ($M = 166.33$ ms, SD = 8.61) faces: $F(1,26) = 18.67$,

[4]Due to the difficulty of perceiving a Mooney face in the inverted position, 20 trials were considered a reasonable cut-off.

Table 4 | P100 Mean (SD) amplitude and latency per condition and electrode.

	Mooney						Photographic					
	Upright			Inverted			Upright			Inverted		
	O1	OZ	O2	O1	OZ	O2	O1	OZ	O2	O1	OZ	O2
Latency (ms)												
Low schizotypy	103.08	98.62	102.38	106.38	97.23	101.00	102.08	100.23	101.85	105.92	97.38	102.92
	(11.28)	(6.61)	(11.36)	(12.43)	(8.08)	(12.39)	(9.10)	(9.86)	(8.74)	(7.57)	(9.28)	(7.94)
High schizotypy	107.21	94.29	104.93	108.79	97.00	106.43	100.50	101.07	101.43	102.93	95.50	101.21
	(9.70)	(7.15)	(11.50)	(9.56)	(8.27)	(10.77)	(8.22)	(8.90)	(7.60)	(9.44)	(8.21)	(6.34)
Amplitude (μV)												
Low schizotypy	6.75	2.59	5.31	6.84	2.46	6.50	8.62	3.75	7.91	8.56	4.90	8.31
	(3.72)	(2.70)	(2.19)	(2.95)	(2.45)	(3.33)	(3.56)	(3.19)	(3.04)	(4.23)	(3.72)	(2.99)
High schizotypy	5.66	2.61	5.24	5.84	2.61	6.36	6.26	2.80	6.03	6.67	3.90	6.73
	(2.79)	(2.53)	(2.41)	(2.79)	(2.31)	(3.48)	(3.21)	(2.64)	(2.72)	(3.34)	(2.42)	(3.16)

Low schizotypy (n = 13), high schizotypy (n = 14).

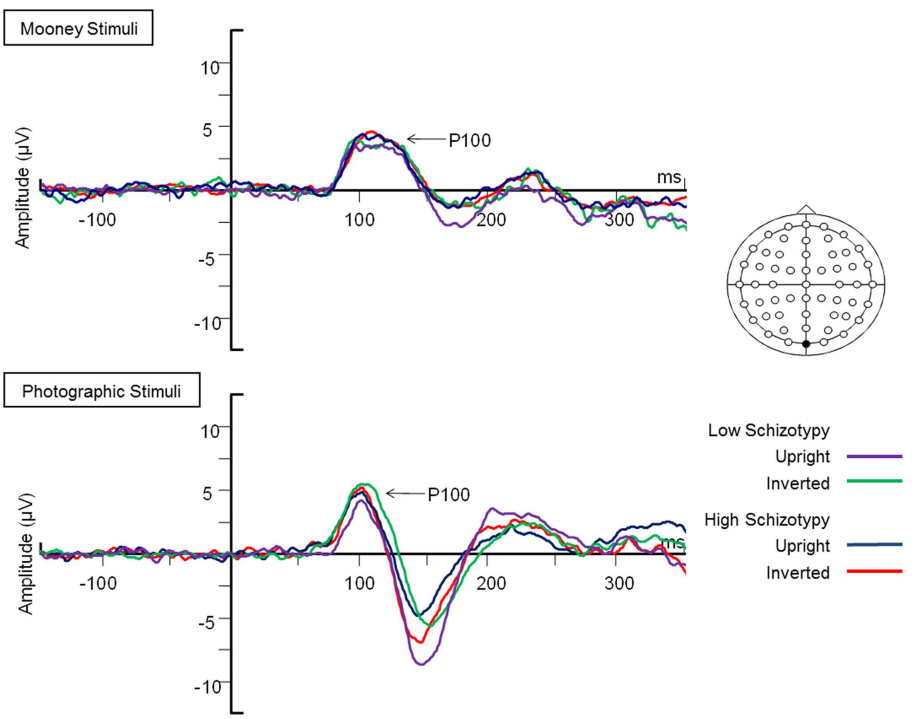

FIGURE 1 | Grand-averaged P100 waveforms at electrode OZ. Upright and inverted stimuli presentations across groups are compared for both tasks. A bird's eye view of the electrode montage is shown with the plotted electrode shaded black. Negative polarity is plotted downward.

$p < 0.001$, $\eta_p^2 = 0.85$. A task × orientation interaction demonstrated similar latencies to upright and inverted Mooney faces, whereas upright photographic faces were marked by earlier latencies relative to inverted photographic faces: $F(1,26) = 8.83$, $p = 0.006$, $\eta_p^2 = 0.85$ (see **Table 5**). The left hemisphere showed earlier latencies ($M = 162.54$ ms, SD = 9.54), than the right ($M = 163.50$ ms, SD = 9.09) to upright faces, whereas this effect was reversed for inverted faces where earlier latencies were shown in the right hemisphere ($M = 165.20$ ms, SD = 9.38) versus left ($M = 167.46$ ms, SD = 9.36): orientation × hemisphere interaction, $F(1,26) = 4.69$, $p = 0.04$, $\eta_p^2 = 0.85$. While there was no main effect for schizotypy group ($p = 0.63$), a group × orientation interaction was shown. The low schizotypy group had earlier latencies for upright relative to inverted faces; however,

Table 5 | N170 Mean (SD) amplitude and latency per condition and electrode.

	Mooney				Photographic			
	Upright		Inverted		Upright		Inverted	
	PO7	PO8	PO7	PO8	PO7	PO8	PO7	PO8
Latency (ms)								
Low schizotypy	173.57	174.64	179.86	177.14	151.79	150.79	158.64	157.29
	(12.07)	(9.83)	(11.27)	(13.33)	(7.91)	(10.37)	(9.13)	(11.50)
High schizotypy	173.79	176.29	173.29	168.43	151.00	152.29	158.07	157.93
	(11.90)	(14.13)	(13.50)	(10.79)	(15.37)	(15.33)	(11.68)	(9.96)
Amplitude (μV)								
Low schizotypy	−6.13	−6.78	−5.25	−5.25	−8.10	−8.79	−11.21	−12.89
	(3.81)	(3.61)	(4.13)	(4.46)	(4.91)	(3.77)	(3.98)	(4.12)
High schizotypy	−3.98	−4.08	−3.96	−4.07	−6.55	−7.57	−8.02	−9.55
	(3.34)	(3.69)	(2.36)	(2.85)	(4.46)	(6.19)	(4.56)	(6.01)

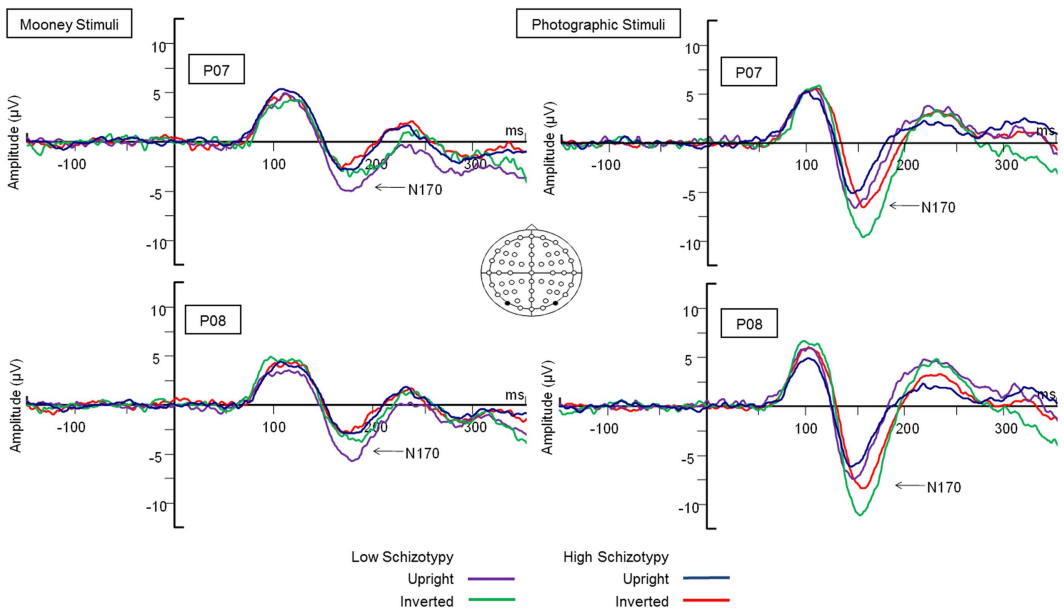

FIGURE 2 | Grand-averaged N170 waveforms at electrodes PO7 and PO8. Upright and inverted stimuli presentations across groups are compared for both tasks. A bird's eye view of the electrode montage is shown with the plotted electrodes shaded black. Negative polarity is plotted downward.

the high schizotypy group had comparable latencies across orientations: $F(1,26) = 8.41$, $p = 0.007$, $\eta_p^2 = 0.85$ (see **Table 5**; **Figure 3**). A task × orientation × group interaction was at trend level ($p = 0.067$).

Amplitude. Greater N170 amplitude was shown to photographic ($M = -9.08\,\mu V$, $SD = 4.34$) than to Mooney ($M = -4.94\,\mu V$, $SD = 3.36$) faces: $F(1,26) = 46.18$, $p < 0.001$, $\eta_p^2 = 0.85$ and to inverted ($M = -7.53\,\mu V$, $SD = 3.48$) relative to upright ($M = -6.50\,\mu V$, $SD = 3.71$) faces: $F(1,26) = 18.23$, $p < 0.001$, $\eta_p^2 = 0.85$. A task × orientation interaction also demonstrated that N170 amplitudes were greater for upright Mooney faces (relative to inverted), however, amplitudes were greater for inverted photographic faces (relative to upright): $F(1,26) = 22.15$, $p < 0.001$, $\eta_p^2 = 0.85$ (see **Table 5**). Furthermore, amplitudes were comparable across hemisphere for Mooney faces in both orientations, but greater in the right hemisphere for photographic faces, especially in the inverted orientation: task × orientation × hemisphere interaction, $F(1,26) = 4.70$, $p = 0.04$, $\eta_p^2 = 0.85$ (see **Table 5**). Again, while there was no main effect for schizotypal group ($p = 0.12$), a group × task × orientation interaction was shown: $F(1,26) = 4.87$, $p = 0.04$, $\eta_p^2 = 0.85$. The low schizotypy group demonstrated increased amplitude to upright versus inverted Mooney faces and substantially increased amplitude to inverted versus upright photographs. However, the high schizotypy group

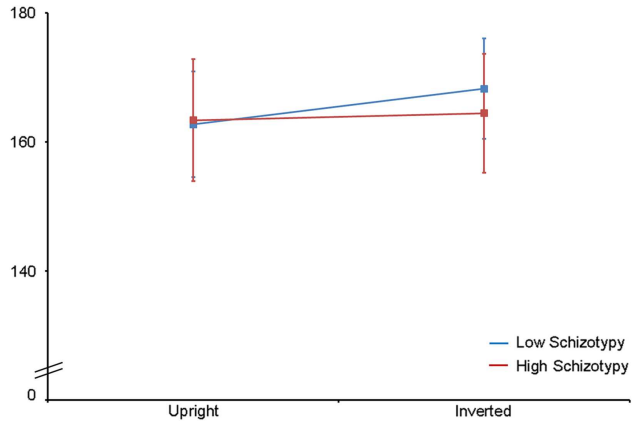

FIGURE 3 | N170 latency group × orientation interaction effect. Comparable peak latencies are shown to upright stimuli by both groups, however, high schizotypes show earlier peak latencies to inverted face stimuli (most difficult to perceive).

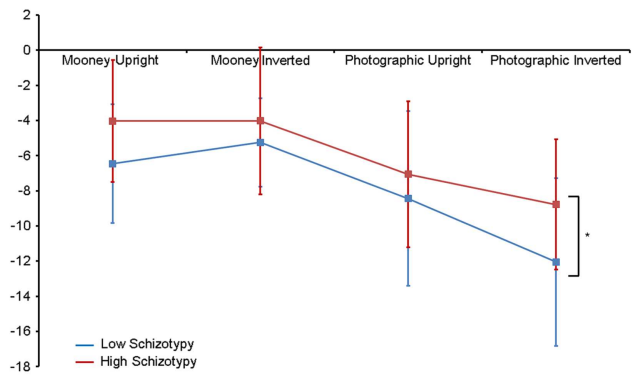

FIGURE 4 | N170 amplitude group × task × orientation interaction effect. Both high and low schizotypes showed the typical inversion effect to photographic stimuli: larger N170 amplitude to inverted versus upright photographic faces (although this difference is smaller for the high schizotypes). However, only low schizotypes showed an inversion effect to Mooney faces (reversed: smaller amplitudes to inverted compared with upright Mooney faces). High schizotypes instead showed comparable amplitude to Mooney faces irrespective of orientation. Note the overall trend for reduced amplitudes in high schizotypy. *$p = 0.05$.

demonstrated comparable amplitude to Moony faces in both orientations, and only marginally increased amplitude to inverted versus upright photographs (**Table 5**; **Figure 4**). *Post hoc* analyses using independent sample t-tests were run on the accumulated N170 mean amplitude [i.e., (PO7 + PO8)/2] for Mooney upright, Mooney inverted, photographic upright, and photographic inverted, separately. The high schizotypy group showed significantly reduced N170 amplitudes for inverted photographic faces only; $t(26) - 2.02$, $p = 0.05$, $d = 0.77$ (Mooney upright, $p = 0.07$, Mooney inverted, $p = 0.35$, and photographic upright, $p = 0.43$).

ERP CORRELATIONS WITH O-LIFE SCORES

Oxford–Liverpool Inventory of Feelings and Experiences scores from the entire sample ($n = 28$) were negatively correlated with the latency of the N170 for inverted Mooney faces, where higher scores (i.e., greater schizotypy) was associated with earlier peak latency for the inverted Mooney faces ($r = -0.38$, $p = 0.05$). No other correlations were significant.

DISCUSSION

N170 latency and amplitude main effects reflected the established literature (14, 45, 46), that is, earlier N170 latencies were demonstrated to photographic (relative to Mooney) and upright (relative to inverted) faces. This typically indicates the more efficient information processing of stimulus categories that are easier to perceive (i.e., photographic and upright faces). N170 amplitude was also larger to both photographic (relative to Mooney) and inverted (relative to upright) faces. The interaction effect clarified that peak amplitudes were greater for upright compared with upside-down Mooney faces, whereas the opposite was true for photographs: these showed the classic inversion effect of larger amplitude to upside-down compared with upright photographic faces. These amplitude effects are discussed in detail with respect to the schizotypal group differences [for more information, see (14, 45)].

Our data demonstrate that individuals high in schizotypal traits show significantly reduced N170 amplitudes to inverted photographic faces. This finding is consistent with the limited N170 literature in schizophrenia (34, 49, 63, 67, 71), and in at-risk individuals (53) where emotional face stimuli has been used. A similar, though non-significant, pattern of reduced N170 amplitude was demonstrated for the remaining three face categories (upright photographic, and upright and inverted Mooney). It is unclear why these categories did not reach significance. In a study using comparable stimuli to ours, Schwartzman et al. (55) also reported no N170 amplitude differences between individuals with high and low proneness to visual hallucinations. However, as the authors suggest, this is probably because deficits in hallucination-prone individuals are more likely to be visuo-sensory specific (as was reflected by P100 differences in their sample), and less likely to be face-specific. In schizotypy, however, neurocognitive deficits in attention, perception, social anxiety, and cognitive disorganization are shared with patients, making them more liable to face-specific deficits (88, 90). Neural processing anomalies shared by healthy individuals prone to psychosis, which are likely to be reduced in degree, may only be detected where effects are especially robust. In our study, this was demonstrated to inverted photographic faces, which are renowned for eliciting a strong amplitude response (14, 26, 43, 47).

Individuals low in schizotypal traits demonstrated the classic increase in amplitude to inverted relative to upright photographs, and an increase in amplitude to *upright* relative to inverted Mooney faces. This latter amplitude effect to Mooney faces has been shown previously, especially on trials where stimuli are recognized as a face (45, 46), which was also the case here. It has been proposed that upright photographic faces engage all three stages of configural processing; first-, holistic, and second-order (14). However, when upside-down, configural processing is

disrupted and these faces are processed analytically (i.e., a part by part process using their featural information), which explains the reliably demonstrated increase in N170 amplitude in response to inversion (45). Similarly, Mooney faces containing configural (holistic/gestalt) information are only processed holistically when presented upright, accounting for a smaller N170 amplitude when compared to upright photographs. Upon inversion, however, featural information is unavailable in the Mooney face, and so analytic processing is not engaged. The subsequent difficulty of processing Mooney faces holistically when upside-down is demonstrated by the reduction in N170 amplitude (45). These typical N170 effects were expected from individuals low in schizotypal traits, and are further reflected by their earlier N170 peak latencies to upright compared with inverted faces, indicating faster face processing to upright faces.

By contrast, the high schizotypes in our study demonstrated comparable N170 amplitude to Mooney faces in both orientations, only marginally increased amplitude to inverted versus upright photographs, and comparable peak latencies across orientations to both face types. Face processing for the high schizotypes was thereby significantly less affected by orientation. Thus, this group was less affected by the disruption to configural information processing in inversion, supporting the established generalized bias for local as opposed to global perceptual processing in schizophrenia (10, 11, 13), and in psychosis prone individuals (12). This is further suggested by the relationship shown between N170 latency and O-LIFE scores for inverted Mooney faces, which indicated that the speed of information processing (latency) increased as schizotypal traits increased. Inverted Mooney faces are the most difficult stimulus category to perceive because configural information is disrupted but alternate featural processing cannot be engaged. The fact that schizotypal traits are associated with faster processing of these stimuli demonstrate further that face processing in high schizotypes is less reliant on configural processing. The generalized poor recruitment of configural information processes may further explain the overall trend for reduced N170 amplitude in this group. However, their neural response to the photographic stimuli suggests that while high schizotypes may have a bias for featural/local processing, they may not be expert in this method of processing either. If this were the case, expertise in part by part analytic processing should be shown electrophysiologically in this group in response to photographic faces. According to the existing literature, a typical, but enhanced, spike in N170 peak amplitude would be expected, and would likely exceed that of the low schizotypes in both orientations. Instead, high schizotypes showed the opposite of this: generally (though non-significantly) reduced amplitude to upright photographs and significantly reduced amplitude in response to photographic faces presented upside-down.

The P100 component is sensitive to changes in luminance and contrast (96). Thus, larger P100 amplitudes to photographic faces in our study reflects added visuosensory input compared with that of the basic black and white shaded Mooney face. Latinus and Taylor (14) have previously reported no differences in P100 latency or amplitude between photographic and Mooney face stimuli, although, they did observe an amplitude decrease to schematic faces, which supports this interpretation. In our study, the demonstrated sensitivity of P100 to orientation (i.e., reduced amplitude and increased latency for inverted versus upright stimuli) is less intuitive. Stimulus characteristics remain consistent across orientations, with more advanced stimulus discrimination not generally shown until later time windows [e.g., N170, N250; see Ref. (37)]. However, P100 may also be modulated by the allocation of attentional resources (70, 96), and it would stand to reason that attention may decline for upside-down faces over the duration of the task, which could explain this finding. Importantly, the absence of schizotypal group differences at P100, as well as the lack of relationship between P100 and O-LIFE scores, demonstrates that early visuosensory processing in high schizotypy appears intact.

Despite the aforementioned significant neurophysiological anomalies, our behavioral data reinforced the healthy status of these individuals high in schizotypal traits. Behavioral responses conformed to previous findings for both high and low schizotypes: stimuli easier to recognize (i.e., photographic and upright faces) attracted more accurate and faster responses, with the least accurate and slowest responses demonstrated for faces most difficult to perceive (i.e., inverted Mooney faces) (14, 45, 46, 55). It is not unusual that high and low schizotypes show matched behavioral performance. Semantic priming literature in schizotypy has consistently demonstrated ERP differences in high and low schizotypes that are not reflected behaviorally [e.g., Ref. (92–94)]. It has been argued that this is because behavioral measures capture later stages of processing, by which time anomalies in neural processing have been accounted for in healthy brains [see Ref. (95) for discussion].

In summary, high schizotypes demonstrated impaired face processing (N170 component), which appears to stem from a specific deficit in the configural assessment of faces, as has been shown in schizophrenia. Importantly, however, this deficit seems to be corrected by later processing, as was indicated by behavioral responses. The early visuosensory processing of faces (P100 component) looks to be intact in schizotypy, although, investigation of the P100 response to face stimuli in individuals at various stages of psychosis-proneness would be profitable. To our knowledge, this is the first study to demonstrate that neurophysiological deficits in basic face processing are present in schizotypy. This work thereby adds to the mounting evidence for analogous neural processing anomalies at the healthy end of the psychosis continuum. The N170 deficits shown by high schizotypes in our study were present without the influence of confounds commonly associated with schizophrenia samples: such as repeated hospitalization, long-term antipsychotic therapy, social isolation, chronic neuropsychological profile, and, in many cases, lowered IQ. This confirms that N170 deficits reported previously in schizophrenia samples do not stem from these confounds. The findings further suggest that face processing deficits indexed by the N170 component may constitute neural dysfunction associated with vulnerability for schizophrenia (e.g., an endophenotype). This adds to the developing profile of individuals at a high risk for the disorder and may help facilitate their early detection. Finally, the results provide further evidence of underlying neurophysiological deficits that may contribute to the poor social interaction characteristic of schizophrenia.

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A false-positive detection bias as a function of state and trait schizotypy in interaction with intelligence

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Hallucinatory experiences are by far not limited to patients with clinical psychosis. A number of internal and external factors may bring about such experiences in healthy individuals, whereby the personality trait of (positive) schizotypy is a major mediator of individual differences. Psychotic experiences are defined as associating abnormal meaning to real but objectively irrelevant perceptions. Especially, the ambiguity of a stimulus correlates positively with the likelihood of abnormal interpretation, and intelligence is believed to have an important influence and act as protective against clinical psychosis in highly schizotypic individuals. In this study, we presented 131 healthy participants with 216 15-letter strings containing either a word, a non-word, or only random letters and asked them to report, whether or not they believed to have seen a word. The aim was to replicate findings that participants with high values in positive schizotypy on the trait-level make more false-positive errors and assess the role of stimulus-ambiguity and verbal intelligence. Additionally, we wanted to examine whether the same effect could be shown for indices of state schizotypy. Our results support findings that both state and trait positive schizotypy explain significant variance in "seeing things that are not there" and that the properties of individual stimuli have additional strong effects on the false-positive hit rates. Finally, we found that verbal intelligence and positive schizotypy interact with stimulus-ambiguity in the production of false-positive perceptions.

Keywords: schizotypy, psychosis proneness, psychosis continuum, perception, intelligence

INTRODUCTION

Hallucinatory experiences, especially of an auditory nature, are sometimes erroneously believed to exist only as symptoms of psychosis and, by extension, schizophrenia. A number of studies have shown, however, that such phenomena are not exclusive to clinically psychotic patients, but can be found even in the healthy population; e.g., (1), reports a prevalence of hallucinations of any kind within a large tri-national sample ($n = 13{,}057$) of 38.7%, whereof no relation to specific pathology was found in more than half of the sample. Visual hallucinations were of considerably higher prevalence than auditory hallucinations (3.2 vs. 0.6%) in the entire sample.

Although a number of clinical and non-clinical factors exist that bring on individual hallucinatory experiences in non-psychotic patients [e.g., stress, caffeine, and the interaction of both; (2)], it has been repeatedly shown that the occurrence of such experiences is mediated by personality traits related to schizotypy [e.g., Ref. (3–5)].

On the phenomenological level, hallucinations have been shown not to actually be seeing or hearing, etc., "things that *are not there*," but rather – as proposed by Kurt Schneider – interpreting abnormal meaning(fulness) to truly existent but objectively meaningless stimuli [cited from Ref. (6)]. This definition translates well into the current biological model of psychosis and psychosis-proneness by Howes and Kapur (7), who plausibly argue that *abnormal meaning* comes from top-down cognitive explanations of *aberrant salience* attributed (as a function of a dysregulation of dopaminergic neurotransmission) to, essentially, irrelevant stimuli. The authors also clearly argue that individual differences in dopaminergic (dys)regulation in the healthy population also exist. Thus, these differences explain both the appearance of hallucinations in non-psychotic individuals, as well as a possible biological basis of the aforementioned personality trait of schizotypy/psychosis-proneness.

Within the schizotypy-framework as defined by Claridge (8), high levels in schizotypy are not necessarily pathological but potentially beneficial; a concept Claridge refers to as "benign schizotypy." Especially, when paired with above-average intelligence, which appears to protect high schizotypes against clinical psychosis (9), especially positive schizotypy is associated with creativity (10, 11) and can be found in higher levels in, e.g., artists, novelists, composers, philosophers, etc. [q.v., (9)]. In those cases, where eminent achievers exhibited biographical indices of clinical psychosis, it has to be noted that their major contributions usually preceded their first psychotic episode (12), or that their psychotic conditions had not caused serious disability or, alternatively, interrupted or ended their creative work (13). Thus, it seems that schizotypy (especially positive schizotypy) but not clinical psychosis is linked to benignly being able to see patterns where others see random noise. In the case of signals within noise, highly schizotypic persons have been shown to rely on less information in order to reach conclusions, whereby this *jumping-to-conclusions*-bias does not relate to the quality of conclusions (14–16).

A typical paradigm for the examination of hallucinatory experiences in healthy individuals is the "White Christmas"-paradigm, during which participants are primed with the eponymous Bing Crosby song and then listen to white noise, during which they are asked to press a button every time they believe to hear the song through the white noise. This paradigm has been used repeatedly by others [e.g., Ref. (3, 4, 17)] and has repeatedly shown the number of false-positive hits correlates positively with schizotypic traits. This paradigm is limited, however, as it allows for no modification of the signal-to-noise-ratio (i.e., difficulty), which has been shown to also be important for the occurrence of hallucinatory experiences (18).

Galdos et al. (19) also found a significant increase in the reporting of meaningful speech when, actually, random noise was presented in schizophrenia patients compared to controls. Within the control group, a similar effect was found as a function of positive but not negative schizotypy as well as of familial risk for schizophrenia. Relevant, in this context, are findings by Dubal and Viaud-Delmon (20) wherein self-reported auditory sensitivity was also positively associated with magical ideation.

Regarding other sensory modalities, Fyfe et al. (21) showed that persons high in schizotypic traits were more likely to interpret meaningfulness in the random movement of triangles, and Simmonds-Moore (22) found effects of schizotypic traits to be more pronounced in visual than auditory stimuli. Interestingly, however, in this publication, no main effect of schizotypy was discovered regarding the number of false-positive guesses in both modalities, but high schizotypes showed significantly greater confidence in their false-positive guesses. Similar results have been published by Corlett et al. (23) regarding the confidence in but not the number of false-positive memories. Contrary to these findings, however, Wilson and French (24) found that individuals significantly more often reporting false-positive memories, also had higher scores in schizotypic measures. Also of relevance is the often reported effect that highly schizotypic persons were more likely to display a tendency to say "yes" to ambiguous stimuli in forced-choice paradigms [e.g., Ref. (23, 25, 26)].

The group around Tsakanikos and Reed [e.g., Ref. (18, 27–30)], under the plausible assumption that the link between schizotypy and a false-positive detection bias was not limited to individual sensory modalities (27), thus, created a visual word-detection paradigm. Herein, participants were presented different moving words and non-words and asked to note (a) whether they had seen a "real" word and (b) which word they had seen. Through variations of the paradigm, the instructions or the difficulty of the task, they were able to link positive schizotypy [measured through the *Unusual Experiences*-scale of the O-LIFE (31)] to the tendency to significantly more often see (and also be able to write down) words when in fact non-words were presented. Furthermore, this link was significantly influenced through task-difficulty and instruction-induced expectancy; i.e., schizotypy had the highest influence in instances (a) where a higher rate of true-positive words was expected than was actually presented, (b) where the true-positive rate was actually high, and/or (c) when the task-difficulty was medium. These results suggest that too easy tasks have too high a signal-to-noise-ratio to make "jumping-to-conclusion" necessary and too difficult tasks lack a minimum of actual perceptual input to allow for the emergence of a false-positive detection bias as a function of schizotypy. A significant effect of stimulus-ambiguity was also reported by van Elk (26).

There are, however, some factors that were not examined so far: as briefly mentioned above, the role of intelligence (especially verbal intelligence or vocabulary) can be considered a relevant factor that may potentially moderate or mediate the effect of schizotypy on a false-positive detection bias in a word-detection task.

Furthermore, schizotypic features, although believed to be relatively stable (8), actually show a certain degree of intraindividual variation; although influenced by habitual (trait) schizotypy, the situational (state) proneness for psychotic-like experiences is dependent upon other internal and external factors. In other words, the probability of having a psychotic-like or hallucinatory experience may vary within the same individual; e.g., in response to environmental factors like perceived (social) stress [e.g., Ref. (32) or influences of recreational drugs (33)]. Therefore, the influences of state measures of schizotypy may prove better predictors of a false-positive detection bias than scores in trait questionnaires. Moreover, it can be expected that a combination of both aspects (trait and state), comparable to a diathesis – stress model, would explain the highest amount of variance in false-positive detection.

It was our aim in this paper to incorporate the aforementioned variables into a single experiment and to pose the following research-questions:

1. Can we replicate the findings of Tsakanikos; Reed and colleagues (q.v., above) that unusual experiences (UnEx) as an indicator of positive schizotypy is associated with a false-positive detection bias?
2. Is the false-positive detection bias additionally related to state indices of positive schizotypy and what is the role of perceived stress in this context?
3. What are the influences of signal-to-noise ratio, task-difficulty, and verbal intelligence/vocabulary on the false-positive detection bias?

MATERIALS AND METHODS

SAMPLE

The sample consisted of a total of 131 healthy participants (according to telephone and on-site self-report). Hereof, 27 were male and 104 female (aged between 17 and 73; $M = 27.43$; $MD = 24$; $SD = 10.63$). Participants were gathered through university adverts, personal communications, and newspaper adverts looking for individuals with telepathic or other extrasensory perceptive experiences. Participants were fully briefed during a telephone interview as well as immediately before the experiment; on both occasions, all participants stated not currently suffering or ever in the past having suffered from a psychological or relevant medical condition.

Research was approved by the ethics committee of the German Psychological Association (Deutsche Gesellschaft für Psychologie, DGPs).

SELF-REPORT MEASURES

Trait schizotypy was assessed using the German version of the Oxford-Liverpool Inventory of Feelings and Experiences [O-LIFE;

(34)]; the *Unusual Experiences* (UnEx) scale was used as a measure of positive schizotypy. The O-LIFE consists of 104 items in a yes/no-format. In order to use UnEx as a factor for a multifactorial ANOVA, participants were trichotomized according to the 33rd-percentiles.

State schizotypic or psychosis-like indices were assessed using a translation of the items used by Barrantes-Vidal et al. (32) for experience sampling methodology. These items are based on the Wisconsin Schizotypy Scales (WSS) and, thus, have a slightly different factor-structure than the O-LIFE [q.v., (35)]. We therefore combined items from the "psychotic-like index" with the "paranoid index" to assess state positive schizotypy. Items suited only for use in experience sampling methodology were omitted (e.g., "Since the last beep, I consumed: Food | Caffeine | Medication | Snuff | Alcohol | Cannabis or other drugs"). Additionally, the item "At the moment I am feeling stressed" was added. All state items were coded on a visual analog scale from 0 (not at all) to 100 (completely) and measured immediately before and after the word-detection paradigm. Verbal intelligence/vocabulary was measured using the Mehrfachwahl–Wortschatz–Intelligenz test [MWT-B; (36)]. The MWT-B consists of several sets of five-letter-combinations, whereof one is an actual word. The participant is tasked with identifying the word; the IQ can be extrapolated from the manual depending on the number of true identifications and the individual words that were (not) identified correctly. The MWT-B was specifically chosen, as it measures (verbal) intelligence in a fashion similar to the trials in our paradigm.

All self-report measures were programed as online-versions using the platform suscisurvey.de.

WORD-DETECTION PARADIGM

The paradigm was programed using Matlab (version 4.0.7 with Psychtoolbox 3.0.9). The paradigm consisted of 216 trials, each preceded by a fixation cross randomly shown between 1 and 2 s. Stimuli consisted of a 15-letter sequence presented in Arial (font size 24; white letters on black background) at a distance of 50 cm between the participant and the computer monitor. Testing was performed on two computers with identical monitors with equal settings; room illumination was kept at a constant level using window blackouts, and participants were alone in the room during the paradigm.

Stimuli were presented for 750 ms each, followed by the question "Did you see a word?" (with yes/no-format). If the participant answered "yes," a second question "Please type in the word you have seen" appeared. Thereafter, the participants were instructed to return to their upright-seated position and press the space-bar for the next trial to commence. Initially, four instruction trials were presented, the first containing a true word and the second not containing a true word (presented for 5 s), the third and fourth instruction trials again with a true word and no word, but presented for 2 s. These stimuli were not used during the main paradigm.

Since the words were German, they are not presented within the scope of this English manuscript. Interested researchers are, however, encouraged to contact the corresponding author.

Of the 216 experimental trials, 72 contained a true word (of five-letter length), 72 a non-word designed according to the corresponding true word using the non-word generator *Wuggy* (37) and the final 72 stimuli containing neither a true word nor a non-word. The true words were gathered from a list of 98 German five-letter words that fit certain criteria (i.e., they were singular-case common nouns that contained no umlaut). These 98 words were randomly embedded into 10 other nonsense letters and given to a sample of 242 unrelated students during a lecture at the University of Applied Science, Giessen, by the principal author. The student were asked to rate the word from "easy to detect" to "difficult to detect" (5-point Likert scale) without time limit. From this, average difficulties were calculated and the 12 "easiest" as well as the 12 "most difficult" words were chosen for the paradigm at hand. For each of these 24 words, a corresponding non-word was created. Words and non-words were each presented three times, namely once at the beginning, the middle, and the end of the 15-letter stimulus (e.g., **HEART**ZBKMLPTWFG, ZBKML**HEART**PTWFG, and ZBKMLPTWFG**HEART**; English word and bold print used just here for clarity). Presentation-order was randomized for each participant, but each participant was presented all 216 stimuli.

Responses were coded by hand (and double-checked by an independent persons) into either of four categories; namely, true-positive, true-negative, false-positive, and false-negative. With respect to the aim of these particular study questions, the categories other than false-positive as well as the reactions times shall not be used as dependent variables within this publication.

STATISTICAL ANALYSES

All statistical analyses were performed using SPSS (version 15). Due to reported effects of age and sex on UnEx [q.v., Ref. (31, 34)] respective variance was removed for between-subject analyses using the generalized linear model by saving standardized residuals and assigning these to the dependent variables. A similar approach was used for the false-positive hit rate in case of significant effects of factors not related to our research question (e.g., age, intelligence).

For within-subject analyses (i.e., influences of word difficulty and -position as well as signal-to-noide ratio), a dependent-samples GLM-analysis was performed with raw false-positive hits as dependent variables in a 2×3-design (two steps for difficulty; three steps for position). A second dependent-samples GLM-analysis was also performed for the analysis of effects of the signal-to-noise ratio on the false-positive hits. This was operationalized through the trial-condition (word, non-word, random letters); with increasingly fewer semantically interpretable entities (word > non-word > random letters) the signal-to-noise ratio was expected to decline.

For between-subject analyses (i.e., influences of schizotypy), an independent-sample GLM-analysis was performed with the standardized residuals of the false-positive hits (independently of difficulty or position) as dependent variables and the trichotomized UnEx-group as factor.

For the analyses of the effects of state schizotypic indices and stress, linear regressions were performed with the standardized residuals of the false-positive hits (again, independently of difficulty and position) as dependent variables and the positive schizotypy index and the stress-item as regressors.

In case of replication questions (i.e., the effects of trait or state positive schizotypy on the false-positive detection rate), one-tailed testing was called for Ref. (38); for all other analyses, two-tailed testing was performed.

Data were controlled for outliers, whereby for the effects of positive schizotypy on the false-positive detection rate one case was eliminated; for all other analyses, it was not necessary to remove this case.

RESULTS

Over the total of 216 trials, our 131 participants reported an average of 5.45 (SD = 4.93) false-positive hits. The range was from 0 (four participants) to 37 (one participant), whereby the latter was considered as the aforementioned outlier, as the next highest number of false-positive hits was 26, followed by 19, and then continuously from 16 through 0. The median was four and there were two modes (1 and 3, with 18 participants each); the second highest number of false-positive hits was four (14 participants). This appears to be substantially higher than in comparable studies by Tsakanikos and colleagues [e.g., Ref. (18)].

The first question was, whether state and trait positive schizotypy had significant influences on the false-positive detection rate. For these analyses, the age- and sex-corrected UnEx-scores were used as dependent variables (in the ANOVA, the sample was trichotomized as described above). Dependent variable was the false-positive detection rate, corrected (as described above) for confounding factors (i.e., intelligence, age, etc.).

We found a significant effect of UnEx (positive schizotypy) on the false-positive detection rate [$F_{2,\,127} = 3.01$; $p = 0.027$ (one-tailed)], whereby Bonferroni-corrected *post hoc* test showed that this effect was mainly explained by the highest scores in the high schizotypy group compared to the low schizotypy group [$p = 0.032$ (one-tailed)].

The regression of state positive schizotypy was also significant [$\beta = 0.254$; corrected $R^2 = 0.057$; $F_{1,128} = 8.85$; $p = 0.002$ (one-tailed)]. Perceived stress had no significant predictive power regarding the false-positive hits; the interaction with state positive schizotypy, however, was significant ($\beta = 0.231$; corrected $R^2 = 0.046$; $F_{1,128} = 4.72$; $p = 0.008$).

The effects of word-position and word difficulty were analyzed using a within-subjects model with Greenhouse-Geisser correction on the false-positive hits (uncorrected for between-subject confounders). Both main effects as well as their interaction were significant; i.e., word-position ($F_{1.8,\,243.46} = 9.16$; $p < 0.001$; partial $\eta^2 = 0.066$), word difficulty ($F_{1,130} = 20.01$; $p < 0.001$; partial $\eta^2 = 0.133$), and interaction ($F_{1.87,243.49} = 6.49$; $p = 0.002$; partial $\eta^2 = 0.048$). Descriptive statistics showed higher false-positive hits with difficult compared to easy words. Regarding word-position, with easy words the rate of false-positive hits was lower when the word was presented at the beginning of the 15-letter string compared to the middle or end. In the hard word category, false-positives were identical when the word was presented at the beginning or end, but higher when the word was presented in the middle. Over all, the highest and lowest false-positive hits were difficult words presented in the middle and easy words presented at the beginning, respectively.

Both main effects as well as the interaction were no longer significant when IQ was introduced into the model as a covariate; thus, suggesting that verbal intelligence moderates the effects of word-position and -difficulty. It has to be mentioned that an interaction between the within- and between-subject factors in one model could not be analyzed, since the within-subject design did not allow for correction of between-subject confounders, whereby the between-subject design necessitated a correction for between-subject confounders. Using between-subject factors as covariates and, apparently, "correcting" for these factors, is, in fact, not a probate method in this case (39).

When positive schizotypy was entered as a covariate, the main effect of difficulty and the interaction between position and difficulty remained significant, albeit with reduced effects sizes (difficulty: $F_{1,\,129} = 5.65$; $p = 0.019$; partial $\eta^2 = 0.042$; interaction: $F_{1.88,\,241.87} = 4.27$; $p = 0.017$; partial $\eta^2 = 0.032$). Additionally, although the main effect of position was no longer significant, there was a significant interaction between position and positive schizotypy ($F_{1.82,\,234.75} = 3.327$; $p = 0.042$; partial $\eta^2 = 0.025$). This effect was the only one that remained significant (with the same effect size), when both IQ and UnEx were simultaneously entered as covariates.

In case of the effect of the signal-to-noise-ratio (operationalized through "condition": word, non-word, random letters) the main effect was significant ($F_{1.68,\,217.84} = 102.81$; $p < 0.001$; partial $\eta^2 = 0.442$), showing similar false-positive hits in the conditions with the highest and lowest signal-to-noise ratio (word and random letters) but an increased detection bias in the non-word condition. The effect remained significant but of reduced size when UnEx, IQ, and both were entered as covariates into the model (respectively: $F_{1.69,\,218.1} = 22.67$; $p < 0.001$; partial $\eta^2 = 0.149$, $F_{1.68,\,216.63} = 4.34$; $p = 0.019$; partial $\eta^2 = 0.033$ and $F_{1.7,\,217.07} = 3.86$; $p = 0.029$; partial $\eta^2 = 0.029$). There were no significant interactions between condition and either positive schizotypy or IQ.

DISCUSSION

We found a significant effect of positive schizotypy on the false-positive detection rate, whereby especially highly schizotypic participants had more incidences of "seeing words that were not there" than low schizotypic individuals. This result is in complete agreement with the findings reported by Tsakanikos and Reed (27, 28). Due to the complexity of the other additionally analyzed factors in this study, we chose not to examine the effects of other schizotypy facets or other performance indices (i.e., true-positives and -negatives as well as false-negatives and reaction time) within the scope of this paper for reasons of brevity.

Additionally, we found that not only trait but also state schizotypy, as assessed through the items used in ESM-studies by Barrantes-Vidal et al. (32), significantly predicted the false-positive hits and interacts with self-reported stress. The latter, in and of itself, did not have predictive power regarding the detection bias in our paradigm. Thus, it would seem that the effects of stress moderate the influence of state schizotypy. This is in line with the supposition that stress (or stressful life events) not only act as facilitators of *inter*individual differences in schizotypy or

psychotic-like experiences [e.g., Ref. (40)] and *intra*individual differences [e.g., Ref. 32)] but also that highly schizotypic persons are more susceptible to stress (41).

In within-subject designs, we found significant effects of the difficulty of the presented word and the position thereof as well as the interaction of both of these factors. Presenting words that had been rated as difficult to detect leads to higher false-positive errors than easy words. Furthermore, when words were presented in the middle of the 15-letter string, more false-positive errors were made, independently of word difficulty, than when words were presented at either the beginning or the end of the stimulus. In the interaction, easy words presented at the end of the string lead to the lowest and difficult words presented in the middle of the string to the highest rates of false-positive errors.

Regarding the signal-to-noise ratio, which was operationalized through the task condition (i.e., the relation of semantically interpretable unit to "letter jumble"), we found that the condition with middle signal-to-noise ratio (i.e., non-words) elicited higher false-positive hits than the high or low signal-to-noise ratios (i.e., word and random letters).

These results agree with the proposition by, i.a., Tsakanikos (18) that very easy tasks (e.g., high signal-to-noise ratio, easy words, words that began or ended the 15-letter string) usually require less cognitive "filling in the gaps" and, thus, incur less errors. In the highly difficult conditions, persons would make less false-positive errors as they would have more difficulty to identify potentially semantically relevant units and, thus, be more likely to answer that they had not seen a word. In this case, a follow-up question would be, whether these difficult conditions elicited significantly more false-negative errors. The finding most necessary to discuss, in our opinion, is that in case of the difficult words presented in the middle the high false-positive hits mean that participants made double-errors; i.e., an additional false-negative error, as they had, actually, not identified the presented word correctly. Extrapolated to clinical psychosis, this would be comparable to a situation where a patient, e.g., sees an unknown (but truly existent) face but erroneously interprets this as another person's face or even something else (e.g., the face of a demon). This would explain anecdotal evidence that hallucinations occur more often at night or in the early evening or morning [(42); q.v., patients' statements on schizophrenia.com]. Also in healthy individuals it is obviously more common to "see something" at night or during dusk and dawn.

The influence of IQ in this case is highly relevant and, to our knowledge, examined for the first time in research of this kind in healthy individuals. The introduction of verbal IQ as a covariate into the model completely eliminated the main effects of difficulty and position as well as their interaction and considerably reduced the effect size of condition. This can be interpreted along the same line of argumentation as before. The higher the intelligence, the more it is likely that difficulty and position will no longer influence the false- as well as the true-positive detection rates (especially considering that we specifically chose an intelligence test with the MWT-B that extrapolates IQ from a number of tasks inherently similar to our paradigm). In other words, the capability of identifying a word independently of its position or difficulty will increase with the aptitude for this kind of task (as measured through the MWT-B). Therefore, the main effects and the interaction will be most prominent in participants with (relatively) low verbal IQ and, thus, were to be expected to no longer be significant when IQ was entered as a covariate. Regarding the reduction of effect size of condition by IQ, the same explanation as above holds.

Going back to the supposition that intelligence may be protective in high schizotypes regarding their transition into clinical psychosis (9), our findings may help explain this. We chose an IQ-test that consisted of a task specifically measuring the aptitude to what we were also measuring in our paradigm. If one extrapolates to crystalline or g-factor intelligence in general, one would also expect that this will influence stimulus-processing on a broader range of levels. Thus, it should be expected that highly intelligent individuals experience less ambiguity in perceived stimuli and thus require less top-down cognitive "filling in" of gaps and are, therefore, less prone to (especially bizzare) psychotic experiences. Future studies will be necessary, in order to ascertain the verisimilitude of this supposition.

The effects of schizotypy are also of particular relevance, especially within the scope of this paper. In order to explore this further, we performed individual one-tailed *ex post facto* t-tests between the high and low schizotypy groups for each variety of word difficulty, word-position, and task condition in order to assess where the effect of schizotypy was strongest.

These analyses showed that differences were most pronounced in the non-word condition ($T_{82} = 2.55$; $p = 0.006$) with a trend in the word condition ($T_{82} = 1.5$; $p = 0.068$) and no difference in the random letters condition. Similarly, schizotypy did not explain significant differences when difficult words were presented, but there was a trend in the cases of presentation of easy words ($T_{72.74} = 1.53$; $p = 0.065$). With regards to position, words presented in the middle lead to the greatest schizotypy-dependent differences in false-positive hits ($T_{82} = 1.98$; $p = 0.025$), especially if these words were easy words ($T_{64.76} = 2.31$; $p = 0.012$). Interestingly, however, although there were not schizotypy-dependent differences in the false-positive hits when difficult words were presented or when words were presented at the beginning of the 15-letter strings, there was a trend in case these factors were combined; i.e., high schizotypes had tendentially higher false-positive hits in cases were difficult words were presented at the beginning of the stimulus ($T_{82} = 1.46$; $p = 0.074$). All effects were in the expected direction; i.e., highly schizotypic persons always had higher false-positive hits rates than low schizotypic persons.

These results, on the one hand, show that in the non-word condition, where most false-positive errors were made, these can be explained significantly by individual differences in trait positive schizotypy; this is, again, in agreement with Tsakanikos (18) that schizotypy-dependent differences are most pronounced in middle signal-to-noise ratios. The same goes for the differences explained by schizotypy regarding the false-positive reactions to word presented in the middle of a 15-letter string. Furthermore, although difficult words lead to a higher false-positive hit rate in general, highly schizotypic persons showed significantly, and borderline-significantly more errors in easy words compared to low schizotypic persons. It can, thus, be asserted that the effects of schizotypy (although significant) are less pronounced than those

of the stimuli. This is in line with the repeated findings that (a) any person, independently of schizotypy, can experience psychotic-like experiences when presented with the "right conditions" and (b) that highly schizotypic persons will be more likely to experiences psychotic-like experiences not only in general but especially in situations were low schizotypic persons will not have a psychotic-like experience.

To summarize, we replicated findings that positive schizotypy leads to a "jumping-to-conclusions" bias and that this bias is most heavily pronounced in reaction to relatively highly ambiguous stimuli. Furthermore, we could show that the effects of schizotypy are considerably less strong than those of stimulus-quality and, thus, that schizotypy explains most variance in those conditions that are not of themselves ambiguous enough to lead to errors in judgment in most persons. In other words, ambiguity increases the amount of errors, but highly schizotypic persons require less ambiguity as a facilitator of a false-positive detection bias than low schizotypic individuals.

We extended upon previous findings by showing that (verbal) IQ significantly moderates both a general detection bias as well as the interactions between said bias and trait schizotypy. Furthermore, we showed that not only trait but also state schizotypy significantly predicted false-positive errors. Although both factors correlated significantly in our study [q.v., (32)], an interaction with stress shows that situational psychosis-like experiences in healthy individuals are not solely a factor of habitual schizotypy.

In conclusion, our results further the understanding that hallucinatory experiences in non-clinical individuals are not only a factor of healthy variations in schizotypy but also depend more heavily on the quality of stimulus-perception and cognition as well as (task-specific) cognitive abilities – as shown by the considerable effects explained through verbal IQ.

Over all, we believe that our study presents a significant add-on to other related findings. We replicate previous results and add relevant information regarding, especially, state schizotypy and intelligence. In the future, different variations of paradigms of this sort may be used and, additionally, combined with imaging and psychophysiological methods (e.g., fMRI and EEG). We are also currently in the process of examining the effects of genetic factors in this relation. It could be expected that specific polymorphisms as well as additive effects of different polymorphisms that are relevant to schizotypy may yield further insight. Preliminary results are highly promising, but we chose not to publish these as yet, due to the fact that the number of participants willing to provide a DNA-sample so far is not large enough to reach the statistical power needed for genetic association studies.

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Social connectedness across the psychosis spectrum: Current issues and future directions for interventions in loneliness

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Loneliness, sometimes referred to as "perceived social isolation," is defined as a subjective experience of social isolation. Loneliness has been shown to be related more to the quality of social relationships than to the quantity, and is typically characterized by feelings of social disconnection (e.g., being misunderstood by others). It occurs when there is a discrepancy between desired and actual amounts of social interaction. Humans are a social species and have a fundamental need to belong. Feelings of loneliness have been perceived to be early warning signals of potential threats to psychological health (akin to physical pain in physical health problems). Loneliness is associated with an increased risk of various health conditions (e.g., increased inflammation, decreased immunity) and can occur in transient and chronic forms across the lifespan.

In the last few decades, there has been an increase in scientific studies in loneliness and much of this research stemmed from a social neuroscience approach (see work by Cacioppo). The onset of loneliness is thought to motivate an individual to seek connectedness with others; however, symptoms of mental illness often involve withdrawal from the social world. A growing interest in the relationship between loneliness and mental health disorders is therefore not surprising and was first identified as an important relationship in the late 1950s. Psychoanalyst Frieda Fromm-Reichmann highlighted the devastating impact of loneliness on patients with schizophrenia. In more recent times, researchers have used a neuroscience approach to further clarify the relationship between social withdrawal/isolation and positive symptoms of psychosis (see Hoffman's social deafferentation hypothesis).

The psychological consequences of loneliness, however, remain under examined by researchers. It is plausible, but remains unclear, that loneliness is a transdiagnostic factor across different mental disorders that raises the risk of mental health problems, increases the severity of symptoms, maintains diagnostic status, or all of the above. Loneliness is associated with various mental disorders, including depression, social anxiety disorder, and obsessive–compulsive disorder (1), and most of the research on loneliness and mental health has focused on its relationship with depression (2).

To date, there has been no published study that has developed an evidence-based loneliness intervention in individuals with psychosis. A meta-analytic review of interventions aimed at reducing loneliness in a range of different populations surprisingly included only five studies with individuals with mental health symptoms, and none of the studies were specific to psychosis (3). There is, however, emerging research that highlights the deleterious effects of loneliness in individuals with psychotic disorders. In the second Australian national survey of psychosis ($N = 1825$), 80.1% of adults aged between 18 and 34 years, diagnosed with a psychotic disorder endorsed perceived loneliness; 37.2% of these adults identified loneliness as a barrier to recovery (4). While many psychosocial interventions are aimed at introducing new social supports (e.g., befriending) or providing social skills training (SST) for people with psychotic disorders, there has been no known study that specifically targets loneliness.

LONELINESS AND THE PSYCHOSIS SPECTRUM

Psychotic symptoms occur on a continuum, ranging from the absence of symptoms to the sustained presence of clinically distressing symptoms. The term "delusion-prone individuals" refers to individuals who report delusional ideation but who are not clinically delusional because of a lack of functional impairment or distress associated with their beliefs. One identified delusion-prone group consists of members of particular new religious movements (NRMs). We found that, despite reporting similar levels of delusional ideation to individuals with psychosis, individuals in the NRM group were not as distressed by their beliefs. One factor that may explain this attenuated distress is the nature of the social relationships under study. NRM individuals reported significantly more helpful supports and more crisis supports than individuals with psychosis. Having a strong group identity may be a protective factor against distress (5). Acceptance into a group of individuals who hold similar values is likely to generate feelings of connectedness and increase the chance of having a confidant from whom one can seek support.

The specific dynamics of relationships (e.g., reciprocity) held can further moderate distress associated with delusional ideation. Reciprocity refers to an exchange–style relationship between two

individuals in which both individuals seek support from each other. In our study, participants with psychosis who reported higher relationship reciprocity were significantly less distressed than those who reported lower relationship reciprocity. One possible explanation is that more balanced relationships may promote positive bonds between individuals whereas less balanced (or one-sided) relationships may confer feelings of burden on the helper and guilt on the recipient. To facilitate the development of more balanced relationships, individuals with psychosis may benefit not just from receiving social support but also from opportunities to in turn provide constructive social support in ways that improve their self-esteem.

Connecting with peers and establishing reciprocal relationships in a naturalistic environment (i.e., less structured social settings that can engender hope and spontaneity) are crucial to buffer against distress associated with psychosis. However, there are potential barriers that should be considered, such as co-occurring social anhedonia, social withdrawal, and schizotypy traits associated with psychotic disorders. In our study, participants with psychosis did not report significantly more dissatisfaction with their relationships, despite reporting significantly fewer and less helpful relationships in their network when compared to the delusion-prone group. It is possible that individuals with psychosis may: (a) be unable to identify a need to initiate or maintain friendships due to negative symptoms or maladaptive cognitions about the social world; or (b) be too distressed to meaningfully participate in social interventions due to active symptoms compared to those in remission or those who report subthreshold psychotic symptoms.

FUTURE DIRECTIONS IN INTERVENTIONS FOR LONELINESS

The early stages of a psychotic disorder can be an isolating time for those afflicted and often entails debilitating social consequences. Targeting loneliness is likely to alleviate distress associated with psychotic symptoms. A well-designed intervention is warranted and may be informed by the following guidelines.

ADDRESSING MALADAPTIVE COGNITION IN SOCIAL RELATIONSHIPS

The experience of loneliness has been found to be "socially contagious" within social networks; in other words, lonely individuals are connected to other lonely individuals (6). Connecting lonely individuals with other lonely individuals may not necessarily lead to them creating friendships because they demonstrate thoughts and behaviors that are unconducive to friendship development. This highlights the importance of addressing maladaptive cognitions arising from the ineffective navigation of the social world.

Because of its subjective nature, loneliness is driven (or at least maintained) by biased cognitions related to the social world, including negative interpretations of social interactions and beliefs about others. In a cognitive model of loneliness, maladaptive cognitions are influenced by other processes, including hypervigilance to social threats and various cognitive biases [e.g., memory bias, confirmatory biases (7)]. In brief, lonely individuals are more likely to form more negative impressions and show more punitive behaviors toward others. Lonely individuals actively contribute to the vicious cycle of loneliness through their use of self-protective behaviors and having self-defeating interactions with others, further isolating themselves.

Addressing maladaptive cognitions around pre-existing social networks may be a useful starting point to improving the quality of those relationships. Any social skills deficits that inhibit the quality of current relationships can also be easily identified and quickly addressed. It may be more feasible for those with high avoidance tendencies (e.g., comorbid social anxiety or schizotypy) to improve current relationships rather than develop new relationships.

Another advantage of looking within current social networks is to identify opportunities to develop a confidant relationship with a known individual or to improve the relationship with a current confidant. The absence of confidants has been linked to higher loneliness in a community sample (8). Individuals with first-episode psychosis were less likely to have a confidant than healthy controls (9). Individuals with psychosis tend to confide in a family member (over 40%) as opposed to a friend (over 30%); others reported that they lost their confidant in the previous 12 months (12.7%) or never had one (15.6%). Almost half (over 48%) of those surveyed reported that they needed more friends (4). Developing and/or improving a relationship with a confidant within the existing social network may be a stepping-stone to developing connections with unfamiliar individuals.

USING POSITIVE AFFECT TO ENHANCE SOCIAL BONDS

Lonely individuals, when compared to less lonely individuals, may have the necessary social skills to relate to others but may not readily use or recognize the efficacy of those skills. However, for people with psychosis (a disorder associated with social skills deficits), it may be crucial to incorporate specific components of SST for loneliness to be successfully targeted. For example, SST components that focus on developing positive interpersonal styles may help people with psychosis to establish more stable social bonds with others.

To date, there has been minimal research on the effectiveness of positive interpersonal styles (e.g., sharing successes in day-to-day life) for mental well-being. There is growing interest in positive psychology principles, specifically in the nature of positive affect in individuals with mental disorders. Positive affect appears to be attenuated in individuals with psychosis. Specifically, these individuals were less likely to savor past or future positive experiences, possibly contributing a lack of engagement with others (10). More severe levels of negative symptoms in individuals with psychosis are associated with having fewer friendships (11). A limited ability to savor positive experiences and the presence of negative symptoms should be accounted for when developing a social intervention for individuals with psychosis. One suggestion to combat the effects of negative symptoms is to teach savoring techniques and to improve self-efficacy pertaining to interpersonal behavior skills.

Another way to generate positive affect is to practise interpersonal styles that can be used to enhance social bonds. The concept of capitalization is borrowed from interpersonal styles in romantic relationships.

Capitalization is defined as the ability to seek out others when positive things occur (12). The ability to capitalize and provide constructive responses to positive events may cultivate positive affect and enhance the bonds between two people within a relationship. For example, in romantic relationships, capitalization is associated with higher relationship well-being (e.g., intimacy). The ability to self-disclose is another factor that may have been under examined in current social interventions. Emerging research has indicated that self-disclosure is integral to relationship development; specifically, disclosure reciprocity that is greater and more immediate than not is associated with more liking and closeness in relationships (13).

INCREASE ACCESSIBILITY TO A POSITIVE SOCIAL ENVIRONMENT

Individuals who are connected with lonelier individuals also become lonelier themselves over time, demonstrating the powerful influence of social networks. Lonely individuals embedded in an enriched social environment find it easier to break out of the loneliness cycle than those without such an enriched environment. Unfortunately, individuals with psychosis are well-known to have impoverished social networks, and the ability to connect with others may be further limited by additional environmental factors such as societal stigma. While access to a social environment where one can practise positive social interactions and form strong social bonds with others is more complex for individuals with psychosis, it is not unachievable and will likely mitigate loneliness once established. Researchers can also consider the use of technology, such as moderated online social forums, to reach individuals who find it difficult to participate in a new social environment. Although online communication forms have become the norm are advantageous in terms of accessibility and can be used as a transitional medium toward in-person communication, the caveats to online communication should be noted (e.g., forums should be moderated to facilitate a positive and safe social environment). Regardless of the modality, it is crucial that people with psychosis be given easy access to a naturalistic social environment that engenders hope and spontaneity, and provides a platform where positive relationships can be nurtured (i.e., practise capitalization, and so on).

CONCLUSION

In sum, loneliness hurts. The aversive experience of loneliness, together with well-known physical and mental health risks, justify the development of specific interventions targeting the reduction of loneliness. Unfortunately, the crucial relationship between loneliness and psychosis has been overlooked and under examined. Individuals with psychosis often suffer myriad difficulties that may fuel loneliness. The ability to connect with others is challenged by various factors ranging from the nature of the psychosis presentation (e.g., negative symptoms) to environmental factors (e.g., societal stigma). There is a crucial need to design an empirically sound intervention for loneliness for individuals with psychosis. It is plausible that a well-designed intervention may reduce the risk of developing psychosis, alleviate the distressing experience of acute psychotic symptoms, and reduce the risk of relapse of psychotic symptoms.

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