THE INTERACTIVE EFFECT OF AUTISM TENDENCIES AND PSYCHOSIS PRONENESS ON SALIENCY AND THEORY OF MIND IN THE TYPICAL POPULATION

by

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ABSTRACT

Difficulties with saliency-based selection and the ability to appreciate the perspective of others (mentalizing) are central to both autism and psychosis spectrum disorders. Both disorders can co-occur in the same individual at both the diagnostic and trait levels. It has been hypothesized that their co-occurrence would lead to greater impairment than would be observed in each of the disorders alone. An alternative theory suggests that these disorders are etiologically and phenotypically diametrical, and thus predicts that these disorders would have opposing effects on these abilities. The current thesis examined these contrasting hypotheses using behavioral, eye-tracking and neuroimaging paradigms, in neurotypical adults in whom both autism tendencies and psychosis proneness were assessed in tandem. The thesis provides converging evidence that autism and psychosis tendencies interactively improve mentalizing abilities as well as target selection in the presence of irrelevant salient distractors. This interactive effect is also discerned at the neuronal level where autism and psychosis tendencies diametrically modulate activity within the attentional and mentalizing subdivisions of the right temporo-parietal junction (rTPJ). These findings suggest that co-occurring autistic and psychotic traits can exert opposing influences on performance, resulting in *improvement* possibly by way of their diametrical effects on attentional and socio-cognitive abilities.

~For My Parents~

Mahmoud Ahmad Abed-Alkareem Abu-Akel (R.I.P.)

&

Zohrea Taher Abu-Akel (R.I.P)

These are our works

These works are our souls' display

Remember our works when we have passed away

(Ibn-Khaldun)

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CHAPTER 1

GENERAL INTRODUCTION

INTRODUCTION

In this thesis, I investigate the interactive effect of autism tendencies and psychosis proneness on attentional and socio-cognitive abilities. Research to date has shown that, in both clinical and non-clinical participants, traits for autism and psychosis are associated with poorer performance in social cognition and attention. However, it is far from clear whether autism and psychosis traits yield these effects for the same reasons, not least because it is uncommon for these traits to be assessed in the same participants. There is a dearth of research that addresses the concurrent effect of autism and psychosis on outcome measures. This can be attributed to three main reasons:

(1) The conceptualization of autism and psychosis as distinct conditions has re-enforced the idea that these conditions are mutually exclusive.

(2) The limitation of theoretical accounts that could reconcile the co-occurrence of these conditions, and

(3) The limitations of standard mathematical/statistical models to meaningfully account for the effect of their co-occurrence on outcome measures.

This thesis addresses this gap by conducting the first systematic investigation of social cognition and attention in healthy participants whose traits for autism and psychosis have been characterized. Within these two broad domains, I specifically focus on the ability to appreciate the perspective of others' mental states (or mentalizing), and salience-based selection, which is a key attentional mechanism associated with the ability to bias attention towards (or away from) salient information. These two aspects are major components of human social interaction and communication and are considered core features for both autism and psychosis. Throughout the thesis, the assessment of autism and psychosis in the healthy population rests on the assumption that both autistic tendencies and psychotic proneness exist on a continuum, ranging from typicality to disorder. In this regard, it is important to clarify

that the use of the term psychosis proneness in this thesis is confined to presence of positive psychotic-like experiences which aligns with Meehl's notion of schizotypy (Meehl, 1990) and more specifically, with Claridge's "aberrant perceptions and beliefs" component of schizotypy (Claridge et al., 1996).

The thesis presents a series of studies utilizing behavioral, eye-tracking and neuroimaging paradigms that examine how inter-individual differences in autism and psychosis effect behavioral and brain functioning associated with these domains. The results will have implications for understanding healthy variation in these traits and abilities, and in how clinical autism and psychosis should be understood.

What follows is a brief overview delineating the historical and current debate surrounding the relationship between autism and psychosis, the way this relationship can be conceptualized, and the rationale for conducting this in the healthy population. Importantly, this overview is not meant to be comprehensive or exhaustive, but to familiarize the reader with context upon which this research is based. In this respect, note that each chapter has been written as a self-contained paper, and so contains substantial introductory information relevant to that chapter.

The relationship between autism and schizophrenia spectrum disorders

Schizophrenia and autism spectrum disorders (SSD and ASD, respectively) combined affect approximately 2% of individuals during the course of their lifetime, inflicting a broad range of cognitive, motor and psychosocial abnormalities. Phenotypically, SSD is associated with the presence of core symptoms that have been classified along negative and positive dimensions, with the former denoting the absence of a function and the latter with the presence of abnormal behavior. Negative symptoms include flat or blunted affect, poverty of speech, anhedonia, asociality and avolition. Positive symptoms include the presence of

delusions, hallucinations, disorganized speech, thinking and behavior. On the other hand, ASD is defined by impairment in social communication and social interaction, and by repetitive behavior and restricted interests and activities. Diagnostically, ASD must exclude the presence of delusions, hallucinations, loosening of associations, and incoherence as in SSD, a criterion that has been enforced until very recently—the current diagnostic manual, DSM-5, allows for the additional diagnosis of SSD in individuals with ASD if they present with prominent delusions and hallucinations for a period of one month (or if successfully treated) (APA, 2013). Conversely, social and communication impairments are integral for the diagnosis of ASD, but not for SSD.

While these definitions were meant to categorically distinguish between the two disorders, the relationship between them has been a contentious issue since autism was first described, and current clinical reality suggests that absolute forms of the disorders are in fact not the norm (Lugnegard, Hallerback, & Gillberg, 2015; Nylander, Lugnegård, & Hallerbäck, 2008; Sheitman, Kraus, Bodfish, & Carmel, 2004). Several recent lines of evidence suggest that there are important cognitive, behavioral and neurophysiological overlaps between the two disorders (for recent reviews see (Chisholm, Lin, Abu-Akel, & Wood, 2015; King & Lord, 2011; Sasson, Pinkham, Carpenter, & Belger, 2011)) as well as shared etiologic factors (Carroll & Owen, 2009; Crespi, Stead, & Elliot, 2010b; P. F. Sullivan et al., 2012; S. Sullivan, Rai, Golding, Zammit, & Steer, 2013). This has prompted some researchers to call for the reevaluation of their relationship (Nylander et al., 2008; Sasson et al., 2011), or at least to reconsider their exclusion criteria (Hofvander et al., 2009).

There are many ways by which we can explain the association between ASD and SSD (for a recent review see (Chisholm et al., 2015). However, four models, though not necessarily simultaneously, have dominated the debate regarding the relationship between them (see Figure 1.1). Model A posits that ASD is subsumed in SSD or vice versa, model B

views the two disorders as independent, model C as overlapping, and model D as diametrical. The merit of these models is considered in turn.

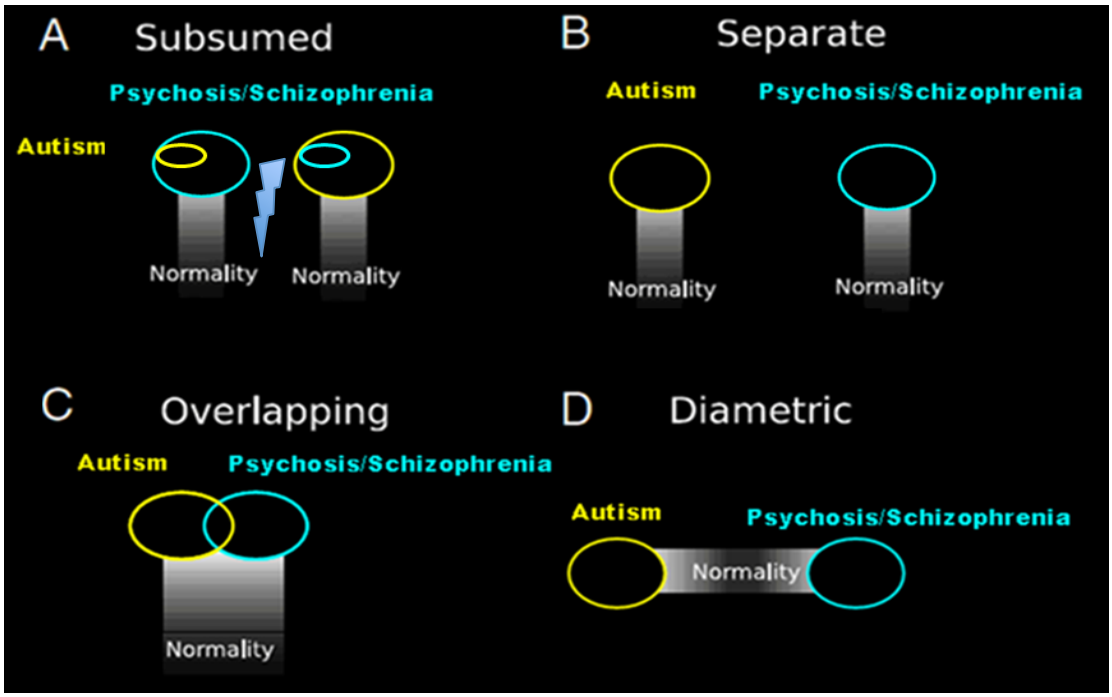

Figure 1.1. Alternative models for the relationship of autism and schizophrenia. (A) Subsumed. (B) Separate. (C) Overlapping. (D) Diametric. (Modified from Crespi et al., 2010). Both ASD and SSD are placed at the extreme of a normality continuum.

Model A which considers autism as a subtype of schizophrenia or vice versa, suggests that autism and schizophrenia could not result from mutually exclusive risk factors. Historically, autism was considered an extreme form of schizophrenia (Bleuler, 1911), and by others as the childhood form of the illness (Bender, 1947). More recently, it has been suggested that ASD-associated brain abnormalities may pave the way for the development of SSD in some patients, based on evidence showing that individuals with ASD who experience psychosis have brains that resemble those of ultra high risk individuals for psychosis (Toal et al., 2009). Under this view, ASD and SSD would necessarily be associated with only a subset of the impairments observed in the other disorder. In addition, this model would predict that individuals having ASD or SSD would necessarily meet the diagnostic criteria for the other disorder, or at least have met it at some point during their etiologic history. However, there is

strong evidence suggesting that ASD can be associated with risk factors that are unrelated to SSD and vice versa (Crespi et al., 2010b). Moreover, the two disorders exhibit neuroanatomical (Cheung et al., 2010) as well as behavioral and cognitive phenotypes that are disorder-specific (Stone & Iguchi, 2011). Accordingly, this model can be ruled out with a great degree of confidence and will not be considered further.

Model B considers the two disorders separate based on evidence showing that ASD and SSD differ in etiology, developmental trajectories and age of onset (Kolvin, 1971; Rutter, 1972). Specifically, based on evidence showing that ASD can reliably be diagnosable by 3 years of age and SSD by late adolescence-early adulthood, the two disorders have been, by consensus, considered separate since the introduction of the DSM-III (APA, 1980)[1]. Under this model, both disorders would exhibit different sets of impairments or pattern of impairments precipitated by independent risk factors or mechanisms. However, as pointed out by several important reviews (Carroll & Owen, 2009; Chisholm et al., 2015; Stone & Iguchi, 2011), both disorders are associated with specific genetic loci or alleles, are highly heritable within and between conditions, share many environmental risk factors such as increased parental age, obstetric complications and urbanicity, and can exhibit similar characteristics such as social withdrawal, poor communication and attentional abilities. There is also evidence suggesting that both disorders co-occur at both the diagnostic (Solomon et al., 2011; Stahlberg, Soderstrom, Rastam, & Gillberg, 2004) as well as at the trait levels (Konstantareas & Hewitt, 2001; Spek & Wouters, 2010). Hence, while both disorders can be viewed as distinct, they are clearly not mutually exclusive and thus this model might be limited in explaining the range of behaviors exhibited in both ASD and SSD. However, this models remains relevant for it dominates current diagnostic practices.

[1] It is important to note that from this point onward, the term *autism* took on a completely different meaning to the way it was originally used by child psychologists: Autism, as defined by Bleuler (1911), was originally used to describe extreme social withdrawal precipitated by excessive fantasies and hallucinations in infants, whereas now autism refers to the absence of the ability to represent life symbolically (Evans, 2013).

Model C posits that the two disorders share overlapping etiologies (Burbach & van der Zwaag, 2009), and thus can feature overlapping phenotypes and exhibit shared areas of deficits (King & Lord, 2011). Indeed, many studies have demonstrated the ASD and SSD can result in similar impairments across several domains (Stone & Iguchi, 2011) including the processing of salient information (Becchio, Mari, & Castiello, 2010; Poirel et al., 2010), theory of mind and perspective-taking (Couture et al., 2010; Craig, Hatton, Craig, & Bentall, 2004), as well as neurocognition and emotional processing (Eack et al., 2013). Collectively, evidence suggests that this model cannot be ruled out as a potential framework to elucidating the nature of the relationship between the disorders and their impact on behavior and cognition.

Lastly, model D posits that ASD and SSD are etiologically and thus largely phenotypically diametrical. Central to this model is that ASD and SSD represent the extreme of a social cognition continuum (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008), wherein autism is associated with underdeveloped social cognition and schizophrenia (at least in the paranoid type) with aberrant hyper-developed social cognition. A prediction of this model is that deficits in both disorders would deviate in opposite directions from normality. Comparative studies lend support to this model and suggest that the disorders are associated with genetic risk factors in a pleiotropic manner (Crespi et al., 2010b), predisposing the individual to developing one disorder or the other. Also commensurate with this model is research showing, for example, that ASD and SSD are diametrically opposed in enhanced versus reduced embedded figure detection (Russell-Smith, Maybery, & Bayliss, 2010), over-selective attention (Reed & McCarthy, 2012) versus reduced selective–attention (Morris, Griffiths, Le Pelley, & Weickert, 2013), convergent versus divergent thinking (Nettle, 2006), as well as in under- versus over-mentalizing (Frith, 2004). Moreover, while the diametric model does not predict diagnostic co-occurrence of both disorders, it does not

rule out co-occurrence at the trait level. For example, in such cases, it is predicted that behavior would be diametrically modulated towards normality by phenotypic traits that are disorder-specific. Accordingly, this model cannot be ruled out as a viable framework to describing the relationship between the two disorders and their effect on behavior and cognition.

Based on the above, the overlapping and diametric models appear heuristically most viable to examining the relationship between autism and psychosis. However, while these models have been conceived to explain the relationship between categorically defined conditions that are either absent or present, genetic- and familial-based studies have led to the reconceptualization of both ASD (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Wing, 1988) and SSD (Claridge et al., 1996; Meehl, 1990) as dimensional conditions, that lie at the end of a continuum that ranges from normality to disorder. The dimensional approach has been endorsed by current diagnostic manuals such as the DSM-5 to complement categorical approaches, as it has been shown to be particularly useful in capturing individual differences in the severity of the disorder and the assessment of comorbidity (Brown & Barlow, 2005). Indeed, it has been argued that modern psychiatry should view the concept of psychotic disorder, and by extension autism, "as a variation of normal human mentation that can be expressed quantitatively" (Van Os, 2010) (p.305). In addition, studying subclinical expressions of ASD and SSD can inform our understanding of etiologic factors, the effect of such expressions on functioning within the healthy population and has the distinct advantage of avoiding the confounds of active symptomatology and medication (Ettinger et al., 2015; Stefansson et al., 2014). As such, the research conducted in this thesis makes virtue of the practical significance and theoretical appeal of the dimensional approach to assessing the relationship between autism and psychosis in the healthy population within the context of the overlapping and diametric models.

Mentalizing and saliency as core features of both autism and schizophrenia spectrum disorders

The conceptualization of ASD and SSD as two distinct conditions and the enforcement of this distinction by diagnostic manuals have led to largely independent bodies of research despite the recognition of similar impairments in both conditions on several domains including attention and socio-cognition. Researchers from both camps have independently proposed that saliency is a candidate endophenotype for both ASD (Uddin et al., 2013) and SSD (Kapur, 2003; Krishnadas et al., 2014). This is supported by studies examining saliency-based selection or related processes such as selective-attention or saliency suppression which suggest that both ASD and SSD are associated with impairments in these abilities (Becchio et al., 2010; Bird, Catmur, Silani, Frith, & Frith, 2006; Poirel et al., 2010; Riby, Brown, Jones, & Hanley, 2012). Aberrant mentalizing abilities have similarly been proposed as a candidate endophenotype of both conditions (Bora, Yucel, & Pantelis, 2009; Chung, Barch, & Strube, 2014; Couture et al., 2010; Sasson et al., 2011). This has been confirmed in several studies that directly compared the two disorders (Couture et al., 2010; Craig et al., 2004; Pilowsky, Yirmiya, Arbelle, & Mozes, 2000) as well as meta-analytically (Chung et al., 2014).

Analytic approach

The centrality of saliency and mentalizing abnormalities in ASD and SSD creates an opportunity where the nature of their relationship between these two conditions can be reevaluated. This evaluation is largely guided by two main assumptions. First, both autistic and psychotic tendencies exist on a continuum, ranging from normality to disorder. This dimensional approach allows us to examine how outcome measures are affected by inter-individual differences in the expression of autism and psychosis traits. Second, ASD and SSD can feature overlapping as well as diametrical phenotypes. Based on the overlapping

model one would expect to see a significant mean effect, whereas based on the diametric model one would expect to see a significant sub-additive/compensatory effect on behavioral and outcome measures. However, while as pointed above, there is sufficient evidence suggesting that ASD and SSD are not mutually exclusive conditions, the separate model (model B, Figure 1.1) remains relevant for it dominates current diagnostic practices. It predicts that ASD and SSD will have independent effects on outcome and behavior. These assumptions guide the statistical models used to analyze the data obtained for this thesis, and specifically the testing of the predictions borne out of the separate (independent), overlapping and the diametric models (models B-D, Figure 1.1).

Thesis Structure

The thesis reports on data from a series of studies that employed behavioral, eye-tracking and neuroimaging methodologies to investigate the interactive effect of autism tendencies and psychosis proneness within the healthy populations. In addition to the introductory chapter (Chapter 1), the thesis consists of 5 empirical chapters and a closing, discussion chapter (Chapter 7). The empirical chapters are written as self-contained manuscripts[2]. The first empirical chapter, Chapter 2, investigates in a large group of healthy adults, the effect of autistic and psychotic tendencies on socio-cognitive functioning. In this study (and the others included in this thesis), autism and psychotic tendencies were assessed with the co-administration of trait-specific, psychometrically dimensional, questionnaires, namely the Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001) and the Community Assessment of Psychic Experiences (CAPE) (Stefanis et al., 2002). Socio-cognitive functioning was assessed by examining perspective-taking abilities within the context of a referential communication task (Apperly et al., 2010; Keysar, Lin, & Barr, 2003), in which participants

[2] While I am aware that theses are traditionally written in the 1st person, please note that the empirical chapters have been written in 1st person plural as they either published, submitted or written in preparation for submission.

are required to follow the instructions of an ignorant co-participant (hereafter, a director). Specifically, the task examines the ability to accommodate the director's requests/instructions based on inferences one should make of the director's state of knowledge. Successful compliance with the director's instructions requires an understanding that the director has a different state of knowledge (or perspective), and a suppression of a prepotent response that is valid only from the individual's perspective. As such, this task can be seen as a proxy of interpersonal communication that relies on efficient use of perspective-taking and theory of mind abilities. This task was chosen since it captures a critical social component of interpersonal communication that relies on efficient use of perspective-taking abilities, which is a core impairment in both autism and psychosis spectrum conditions. In addition, previous studies report high error rates on this task (~40%) (Apperly et al., 2010; Keysar et al., 2003) and thus it is potentially sensitive to inter-individual differences. This study revealed, and for the first time, that the probability of making perspective-taking errors is interactively modulated by the relative expression of autism tendencies and psychosis proneness.

Intriguingly, individuals with low or high balanced autism and psychosis expressions performed at similar levels, and exhibited lower error rates compared to autism-dominant as well as psychosis-dominant individuals. I thus asked, in Chapter 3, whether the low and high balanced individuals are indeed similar. This question is important, because similar error rates do not necessarily imply that low and high balanced individuals process information in the same way. To address this question, we employed in this study a more sensitive version of the perspective-taking task (Wang, Cane, Ferguson, Frisson, & Apperly, 2015) that allows us to examine response times as well as possible information processing differences between the low and high balanced individuals by systematically tracking their eye-movements. A second goal of this study was to replicate our finding from Chapter 2 regarding the interactive effect of autism and psychosis on perspective-taking errors in terms of response

time. This study revealed that while low versus high balanced expressions performed equally well, the high balanced groups were less efficient in working out the perspective of the other. In addition, autism and psychosis had an interactive effect on response times, thus replicating our finding from Chapter 2.

Turning to saliency, Chapter 4 investigated in a large cohort the interactive effect of autism tendencies and psychosis proneness on selective attention and saliency suppression. Specifically, the study investigated how these traits affect the processing of two competing sources of information where one set of information is more prominent (i.e., more readily available for processing) and the other is less prominent but is in fact more relevant to the task at hand. This was investigated in two experiments. The first was Mevorach et al.'s (2009) variant of the Navon's classic global-local task (Navon, 1977), and the second is a novel face-scene perception, developed in the Lab of Dr. Mevorach. Both tasks allow us to test the effect of autism tendencies and psychosis proneness on selective attention and saliency suppression. In addition, the face-scene perception task enables us to test for attentional/perceptual biases to socially relevant stimuli (i.e., faces) as well as whether the effects were perceptual or attentional. Specifically, it enables us to investigate whether the effects of autism tendencies and psychosis proneness are associated with the perception of salient stimuli, or with the suppression/filtering out of competing salient information. Findings from these two experiments provide convergent evidence suggesting that the cost associated with the presence of salient distractor (i.e., saliency cost) is interactively modulated by autism and psychosis expressions.

At this point, the thesis turns focus to the brain with the goal of exploring whether this interaction between autism and psychosis can be discerned at the neuronal level. However, as a necessary initial step, in Chapter 5, I report on an imaging study that investigated in healthy adults how the neural network associated with adopting an intentional stance (i.e., perceiving

agents as rational thinking beings) (Dennett, 1996) is modulated when interacting with other humans or non-humans (e.g., computers), and whether such variations are associated with whether these agents are willful, active agents or passive agents that merely fulfill instructions. Thus, this study is the first to investigate the intentional stance by orthogonally varying perceptions of the opponents' intentionality (they responded actively and freely or passively according to a script) and their embodiment (they were a human or a computer), while playing the famous playground game, *Rock, Paper, Scissors* (RPS). This task was chosen since it has been shown to reliably activate the mentalizing network in a competitive context (Chaminade et al., 2012; Gallagher, Jack, Roepstorff, & Frith, 2002), an thus it is an attractive alternative to language- and cognitively-laden mentalizing tasks (such as the functional localizer task (Saxe & Kanwisher, 2003)), because it is engaging, interactive, and cognitively undemanding.

Results reveal that this task robustly drives activity in the mentalizing network, and particularly in the right temporoparietal junction (rTPJ) and the anterior paricingulate cortex. This finding is confirmed with an overlap analysis with activations obtained from the same participants whilst performing the theory of mind functional localizer task (Hartwright, Apperly, & Hansen, 2012; Saxe & Kanwisher, 2003). However, given that our sample consisted of 24 adults, the study is not sufficiently powered to conduct whole brain analysis as a function of autism and psychosis traits and their interaction. Therefore, in Chapter 6, I conducted a region of interest correlational analyses to examine the effect autism, psychosis and their interaction on neuronal activity within the rTPJ and the anterior paracingulate cortex. With respect to the rTPJ, we investigated these potential effects within specific regions of the rTPJ based on recent advances suggesting that the rTPJ can be divided in to three subdivisions that are functionally linked to the mentalizing, ventral and dorsal

attentional systems. This study provided the first evidence that the interactive effect of autism and psychosis can be captured at the neuronal level.

In closing, Chapter 7 summarizes the main findings of the thesis. I discuss that investigating mentalizing and saliency as a function of the relationship of autism tendencies and psychosis proneness can have profound implications for: 1) the continuity models of psychosis and autism and in particular how healthy variation in the expression of these conditions affect core features, 2) conceptualizing the relationship of autism and psychosis, and more specifically the nature of their interactive effect on these abilities, 3) research concerned with the identification of divergent and/or convergent mechanisms that could explain performance on these abilities in ASD and SSD, and 4) research methods that investigate ASD and SSD, whether comparatively or in isolation. Here I also discuss research limitations and future research suggestions.

CHAPTER 2

PERSPECTIVE-TAKING ABILITIES IN THE BALANCE BETWEEN AUTISM TENDENCIES AND PSYCHOSIS PRONENESS[3]

[3] This chapter is published: Abu-Akel, A., Wood, S.J., Hansen, P.C., Apperly, I.A. (2015). Perspective-taking abilities in the balance between autism tendencies and psychosis proneness. *Proceedings of the Royal Society B: Biological Sciences* 282 (1808). http://dx.doi.org/10.1098/rspb.2015.0563

ABSTRACT

Difficulties with the ability to appreciate the perspective of others (mentalizing) is central to both autism and schizophrenia spectrum disorders. While the disorders are diagnostically independent, they can co-occur in the same individual. The effect of such co-morbidity is hypothesized to worsen mentalizing abilities. The recent influential 'diametric brain theory', however, suggests that the disorders are etiologically and phenotypically diametrical, predicting opposing effects on one's mentalizing abilities. To test these contrasting hypotheses, we evaluated the effect of psychosis and autism tendencies on the perspective-taking abilities of 201 neurotypical adults, on the assumption that autism tendencies and psychosis proneness are heritable dimensions of normal variation. We show that while both autism tendencies and psychosis proneness induce perspective-taking errors, their interaction reduced these errors. Our study is the first to observe that co-occurring autistic and psychotic traits can exert opposing influences on performance, producing a *normalizing* effect possibly by way of their diametrical effects on socio-cognitive abilities. This advances the notion that some individuals may, to some extent, be buffered against developing either illness or present fewer symptoms due to a balanced expression of autistic and psychosis liability.

INTRODUCTION

The relationship between schizophrenia and autism has been a contentious issue since autism was first distinguished from schizophrenia (Kolvin, 1971). While currently conceptualized as separate disorders, several recent lines of evidence suggest that the disorders co-morbidly occur at a higher than expected rate (Hofvander et al., 2009; Nylander, Lugnegård, & Hallerbäck, 2008; Sheitman et al., 2004), and can themselves be mutual risk factors (Crespi, Stead, & Elliot, 2010; King & Lord, 2011; P. F. Sullivan et al., 2012). Both disorders are also thought to exist on extended phenotypic continua (Baron-Cohen et al., 2001; Claridge et al.,

1996; Crespi et al., 2010; Wing, 1988), with overlapping diagnostic (such as deficits in social interaction and communication) and non-diagnostics traits (such as impaired attention and mentalizing). Despite evidence for such overlaps, no studies to date have examined the impact that either diagnostic or trait-level co-occurrence could have on cognition and behavior.

Socio-cognitive difficulties, particularly understanding and using the mental perspectives of others, are a core feature of both disorders, and are variably affected by the degree of their severity (Abu-Akel, 2003; Chung et al., 2014). These abilities are essential for social and linguistic functioning in that they allow us to understand and predict the behavior of others in terms of the state of their knowledge, intentions, beliefs and desires. Thus social cognition is one central domain where the relationship between the two disorders can be evaluated (Sasson et al., 2011).

On the assumption that both autistic tendencies and psychotic proneness exist on a continuum, ranging from typicality to disorder, one approach to evaluating the impact of co-occurring traits on social cognition is by examining the association of autistic tendencies and psychosis proneness among non-clinical populations. This approach allows us to study both schizophrenia- and autism-like socio-cognitive characteristics without the confounding effects of medication or active symptomatology. To this end, the socio-cognitive abilities of 201 healthy adults were examined using Apperly et al.'s (Apperly et al., 2010) variant of the Keysar et al. (Keysar, Barr, Balin, & Brauner, 2000) referential communication task in which participants are required to follow the instructions of "director" characters. Critical trials required the participant to follow requests/instructions from a director who did not know about all of the possible objects in a grid, and participants had to take this into account when interpreting the director's instructions. Relational trials involved three critical objects varying in size or shape (e.g., three sizes of block). In these trials, only two of these three objects

were visible to the director, and participants had to take this into account when following his instruction (e.g., to "Move the large block…"). Ambiguous trials involved two critical objects described with homophones (e.g., a computer mouse and a rodent mouse) of which only one is visible to the director. In both cases, correct responses required participants to ignore a potential referent that was not visible from the director's view, and select a valid referent that was visible to the director (see Methods, Figure 2.1). Thus, successful compliance with the director's instructions requires an understanding that the director has a different state of knowledge, and use of that information to constrain linguistic reference. As such, this task captures a critical social component of interpersonal communication that relies on efficient use of perspective-taking abilities. Psychosis proneness was assessed using the positive scale of the Community Assessment of Psychic Experiences (CAPEp) Questionnaire (Stefanis et al., 2002), and autism tendencies were assessed using the Autism Spectrum Quotient (AQ) Questionnaire (Baron-Cohen et al., 2001).

A natural prediction from the standard clinical conception of autism and schizophrenia as independent disorders (Kolvin, 1971) is that related characteristics in the typical population make independent negative contributions to perspective-taking performance. It follows that co-occurring high levels of these traits should be associated with worse perspective-taking than high levels of either set of traits alone. A recent influential theory, however, hypothesizes that both autism spectrum disorders (ASD) and schizophrenia spectrum disorders (SSD) are etiologically and thus largely phenotypically diametrical (Crespi & Badcock, 2008). Central to this model is that ASD and SSD represent opposite extremes of a social cognition continuum (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008), wherein ASD is associated with under-active mechanistic social cognition and SSD with hyper-active mentalistic social cognition, deviating in opposite directions from typical performance. Such conceptualization would predict that the relative dominance of traits for

either condition would predispose individuals to increased socio-cognitive difficulties. In the event that there is a balance between the two, this model predicts that these socio-cognitive difficulties would be diametrically modulated towards typical performance by co-occurring phenotypic traits that are disorder-specific.

METHODS AND MATERIALS

Participants

The socio-cognitive abilities of 201 healthy adults (43 males, 158 females; mean age (SD) = 21.37±4.32) we examined in this study. Participants were excluded from the study if they had a history of psychiatric illness, epilepsy, neurological disorders, suffered brain injury or may have current alcohol or substance abuse problems. The study was approved by the University of Birmingham Research Ethics Committee, and written informed consent was obtained from each participant.

Procedures

In a quiet room, participants first completed Apperly et al.'s (Apperly et al., 2010) variant of the Keysar et al. (Keysar et al., 2000) referential communication task, followed by completing the Community Assessment of Psychic Experiences (CAPEp) Questionnaire (Stefanis et al., 2002), and autism tendencies were assessed using the Autism Spectrum Quotient (AQ) (Baron-Cohen et al., 2001).

Materials

The Perspective-Taking Task

The task was based on Apperly et al. (Apperly et al., 2010), Experiment 1. In this task, participants are presented with a 4x4 grid that contained 8 cartoon images (Figure 2.1). On

the opposite side of the grid stands a male director, and on the front side a female director who shares the same view as the participant. Five slots of each grid are occluded from the view of the male director, thus creating a different perspective than that of the participant (see Figure 2.1 A-B). The male director is ignorant of the content that these slots may contain. Audio instructions are played to the participant in a male voice (representing the male director) or a female voice (representing the female director). Instructions pertained to moving objects within the grid 'up' or 'down', 'left' or 'right'. Participants were explicitly told to take the perspective of the male director when fulfilling his instructions.

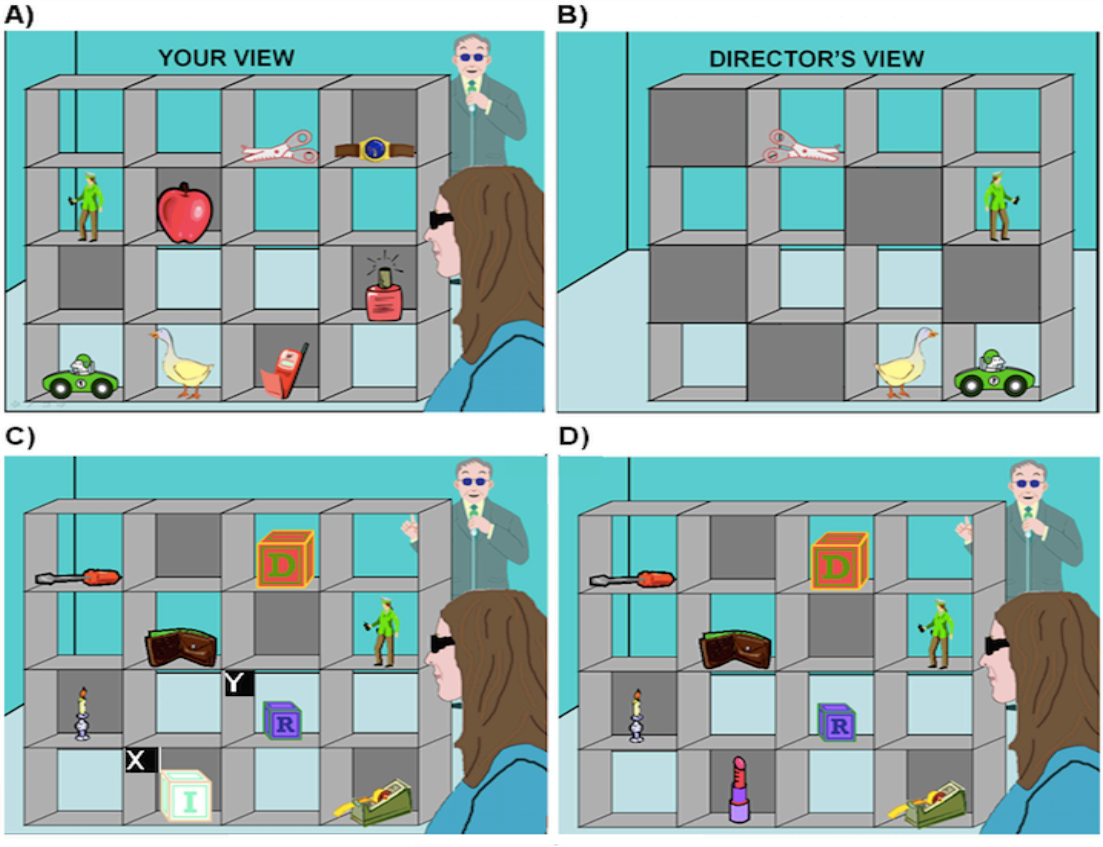

Figure 2.1. (A) and (B) are instruction grids to participants. (C) Experimental relational trial. (D) Control condition of the experimental relational trial.

The task consisted of 32 grids (3-5 instructions/trials each) for a total of 128 trials. Of the 128 trials, 96 trials were fillers and thus are not part of the analyses. The remaining critical trials consisted of 16 experimental and 16 control trials. All the critical trials are spoken by the male director. Instructions given immediately before the critical instructions

were equally often from the male and the female directors. The critical (experimental and control) trials were equally divided into ambiguous and relational trials. The 8 experimental relational trials pertained to objects that are relative to each other either in size or location. Figure 2.1C-D presents an actual example of an experimental relational trial with the matching control. In this trial, the participant is instructed to "*move the bottom block one slot left*." For a correct compliance with the instruction, the participant needs to ignore the distracting block (marked 'X' in Figure 2.1C and which is not available from the view of the director) and move the block marked 'Y'. The control trial contains the same information as the experimental trial except the *block* in the bottom row is replaced with a different object (a lipstick) (Figure 2.1D). In the 8 experimental ambiguous trials (not shown in figure), the noun denoting the object to be moved has two potential referents. For example, '*glasses'* in '*move the glasses one slot to the left*' could be referring to either a pair of reading glasses or a pair of drinking glasses. Only one of these items is available from the view of the male director, as the other 'competing' item is in an occluded slot. In the matching control for this condition, the 'competing' object in the occluded slot is swapped with a different object (e.g., a toy car).

Seated approximately 60cm from a 17" monitor, the session started with two practice grids with non-experimental instructions. The 32 grids of the main experiment were presented in two fixed pseudo-random orders between-participant. The participant always moved the objects from their own perspective with the computer mouse. This was achieved by first clicking on the object and then dragging it with the cursor to the appropriate location. Participants were told that doing this would not actually move the object, but should act and move the mouse as if it did. Each grid appeared for 5 seconds of study time before the instruction was given. The instructions were given at 5-second intervals. Correct responses were recorded if the participant clicked on the object that fit the instruction and could be seen

from both the director's and the participant's perspective. Incorrect responses were recorded if the participant selected the distracter object (i.e., block marked X in Figure 2.1C) or clicked on some other cell. Timeouts were also recorded, but these were not included in the error count. Response times (RTs) were measured from the onset of the noun phrase. Following earlier work we did not expect RTs to reveal condition differences, but they do give the opportunity to examine any tradeoffs between speed and accuracy. This also allows us to examine differences between the corresponding control and experimental conditions. The experiment was run in a single block using E-prime 2.1.

The Community Assessment of Psychic Experiences (CAPE) Questionnaire

This self-report questionnaire is based on the Peters et al. Delusions Inventory-21 (PDI-21) (Peters, Joseph, & Garety, 1999) and consists of 42 items measuring the presence of *positive* psychotic experiences (20 items), *negative* psychotic experiences (14 items), and *depressive* experiences (8 items) that an individual may have experienced over the last 12 months ((Stefanis et al., 2002); http://www.cape42.homestead.com/). The occurrence of these symptoms is reported on a likert frequency scale from 1 (never) to 4 (nearly always), and the associated distress on a scale ranging from 1 (not distressed) to 4 (very distressed). Cronbach's α for this scale in this study is .92, which indicates high internal consistency. For current purposes, the 20-item CAPE positive scale is used as a measure of psychosis proneness. The assessment of positive schizotypy rather than the general construct of schizotypy is based on evidence for autism-positive schizotypy axis in the non-clinical population (Dinsdale, Hurd, Wakabayashi, Elliot, & Crespi, 2013), and that negative symptoms do not reliably discriminate between the ASD and SSD (Spek & Wouters, 2010). The internal consistency of this scale in this study is very good (Cronbach's α = .84), and

falls within the range of values reported in other studies within the general population (Lin et al., 2011).

The Autism Spectrum Quotient (AQ) Questionnaire

This self-report questionnaire consists of 50 items that measure the presence of traits associated with the autistic spectrum within the general population (Baron-Cohen et al., 2001). Each item is given a score of 0 or 1. Higher scores indicate the presence of greater autistic tendencies. The AQ's internal consistency in this study is good (Cronbach's $\alpha = .82$), and is comparable to the values reported in other studies (Austin, 2005).

RESULTS

Before the main analysis, we examined the rate of errors made in the ambiguous and relational trials. On average, participants erred (i.e., failed to appreciate the perspective of the director) on 20.6% of the ambiguous trials and 41.5% on the relational trials. These rates are similar to previous reports using this task (Apperly et al., 2010; Keysar et al., 2003). An examination of the response times showed no evidence of speed-accuracy trade-offs (see Appendix 1, Table 1). Finally, an examination of the association between the CAPEp and AQ scores showed a modest but a significant association ($r=.31$, $p<.001$), which is consistent with the observed phenotypic overlaps between the autism and psychosis spectra (See Appendix 1, Figure 1).

To examine the effect of autism tendencies and psychosis proneness, the participants' perspective-taking (PT) error counts on the ambiguous and relational trials were analyzed using Poisson regression models with negative binomial distribution. Using Generalized Linear Models, we first investigated the association of the participant's PT errors on the relational trials with the AQ scores, the CAPEp scores and their interaction. The omnibus test

shows that the overall model is significant (χ^2 =13.38, df=3, p=.004). The model's parameter estimates (i.e., the main effects and the interaction term) are also significant (see Table 2.1). When entering gender into the model, which is regarded as a relative risk factor for autism and psychosis, the results remained unchanged (Appendix 1, Table 2). Although ambiguous trials showed a far lower error rate, they yielded data with the same qualitative pattern we observed for the relational condition (Appendix 1, Table 3). However, the overall model was not significant when these data were subject to the same analysis as the relational trials (χ^2 =2.91 df=3, p=.406).

Table 2.1. Summary of coefficients with errors on the experimental relational trials as the dependent variable

Model / Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	-1.795	.4299	17.428	1	.166	<.001
AQ	.053	.0233	5.200	1	1.054	=.023
CAPEp	.045	.0156	8.224	1	1.046	=.004
AQxCAPEp	-.002	.0008	4.655	1	.998	=.031

AQ = Autism Quotient; CAPEp = Positive scale of the Community Assessment of Psychic Experiences.

From Table 2.1, we see that an increase in the AQ or the CAPEp resulted in an increase in PT errors. Intriguingly, however, the interaction between these two terms is negatively associated with PT errors. To probe the nature of the interaction term, we follow the method by Hayes and Matthes (Hayes & Matthes, 2009) whereby the effect of one predictor on the probability of committing PT errors (derived from the regression equation) is examined at the mean, one standard deviation below the mean and one standard deviation above the mean of the other predictor. Figure 2.2A visualizes the interaction between psychosis and PT errors by plots of simple regression lines for the participants with low AQ

(10.04), average AQ (AQ=16.33), and high AQ (AQ=22.63), and Figure 2.2B visualizes the interaction between autism tendencies and PT errors for the participants with low CAPEp (CAPEp=22.53), average CAPEp (CAPEp=27.37), and high CAPEp (CAPEp=32.21). The analysis presented in Figure 2.2A suggests that the relationship between psychosis proneness and the increased probability of committing PT errors is significant when the AQ scores were low (−1 SD) (β=0.023, p=0.003) as well as when the AQ scores were at the mean (β=0.013, p=0.004). Conversely, when the AQ scores are high (+1 SD), the relationship between psychosis proneness and PT errors is non-significant (β=0.003, p=0.558). This suggests that individuals with higher psychosis proneness commit PT errors mainly when they have low or average levels of AQ scores. Conversely, high AQ scores seem to have an attenuating effect on the PT errors associated with an increase in psychosis proneness.

In contrast, the analysis presented in Figure 2.2B suggests that the relationship between the AQ scores and the increased probability of committing PT errors is significant only when the CAPEp scores were low (−1 SD) (β=0.011, p=.047). Conversely, when the CAPEp scores are average or high, the relationships between AQ and PT errors are non-significant (β=0.003, p=0.407; β=-0.005, p=0.394, respectively). This suggests that AQ is predictive of PT errors only in participants with low CAPEp scores and that average and high CAPEp scores seem to have an attenuating effect on the PT errors caused by an increase in the AQ scores.

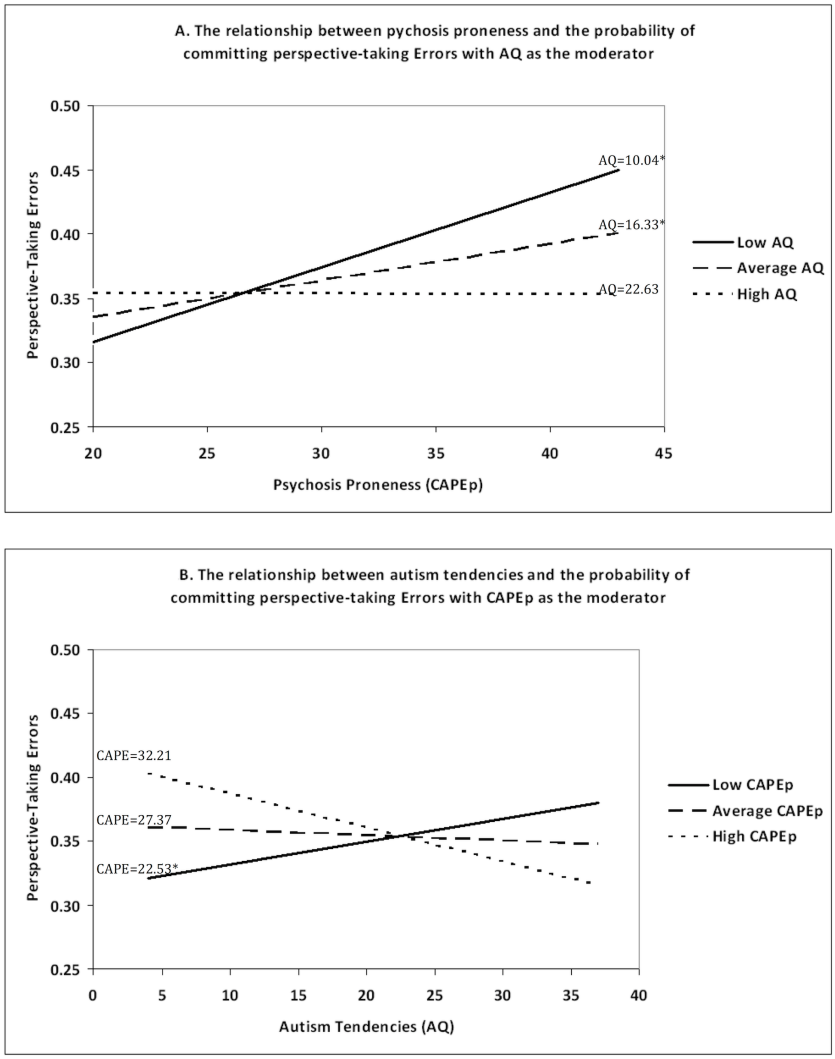

Figure 2.2: A) The relationship between psychosis proneness and the probability of committing perspective-taking errors, evaluated at low, average and high AQ scores. **B)** The relationship between autism tendencies and the probability of committing perspective-taking errors, evaluated at low, average and high CAPEp scores. Asterisks indicate significant slopes.

To estimate if the relative dominance of autism tendencies or psychosis proneness was associated with the occurrence of errors in these trials, the AQ and CAPEp scores were converted into Z scores. A bias score for each participant was then derived by subtracting the CAPEp Z values from the AQ Z values. An inspection of the data suggested a curvilinear relationship between the bias score and the errors in the relational and ambiguous conditions. To investigate this possibility, we entered into the regression model the bias score (AQz-

CAPEpz), the sum of the Z scores of both scales (AQz+CAPEpz), the interaction term of the bias score with the sum of Z scores, and the quadratic terms of the bias score and the sum of scores. The overall model was significant (χ^2 =14.48, df=5, p=.013), with only the quadratic term of the bias being significant (β(±SE) = .021(.001), Waldχ^2 = 4.83, df=1, p=.028). Here too gender had no effect on the model (Appendix 1, Table 4). As can be seen from Figure 2.3, the probability of committing PT errors is associated with the relative dominance of autism tendencies or psychosis proneness, following a U-shape pattern. That is, individuals with elevated tendencies to either autism or psychosis were equally likely to commit PT errors. Interestingly, however, individuals with either high or low tendencies to both autism and psychosis, performed at similar levels. A similar, though non-significant, pattern was also observed for errors in the ambiguous condition (Appendix 1, Figure 2).

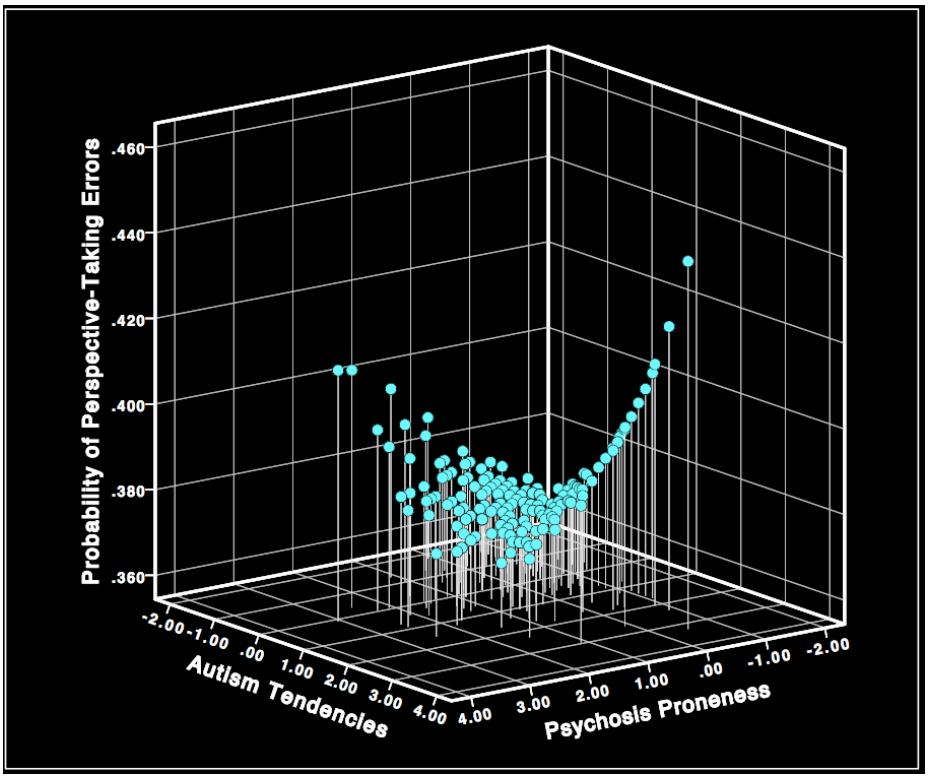

Figure 2.3: 3-D representation of the relationship between autism tendencies and psychosis proneness (represented as standardized Z scores) and the probability of making perspective-taking errors on the relational trials. The negative scores represent low tendencies and the positive scores represent high tendencies.

DISCUSSION

Our study reveals a dose-dependent relationship between autism tendencies and psychosis proneness and mentalizing difficulties. This finding confirms earlier reports showing that both autistic tendencies (Baron-Cohen et al., 2001; Bartz et al., 2010) and psychosis proneness (Fyfe, Williams, Mason, & Pickup, 2008; Gooding & Pflum, 2012; Pickup, 2006) impact perspective-taking and socio-cognitive abilities in healthy adults. Our findings thus provide further support to the continuity/dimensional models of ASD and SSD. They suggest that subclinical manifestations of core features of both disorders are detectable in a healthy population, and that such subthreshold levels can influence socio-cognitive abilities.

Surprisingly, co-occurring autism tendencies and psychosis proneness have a moderating effect on the mentalizing difficulties engendered by either disorders alone (Figure 2.2 A and B), such that the moderating effects are greatest when both tendencies are high rather when both are low. This can be clearly seen in Figure 2.3 where the performance of participants presenting with high tendencies to both disorders is similar to participants presenting with low tendencies to both disorders. Thus the association of the interaction between autistic tendencies and psychosis proneness with a decrease in mentalizing difficulties can be seen as support for the diametrical model (Crespi & Badcock, 2008), which posits that autism and schizophrenia have opposing effects on behavior and cognition.

Whether the errors we observe, as would be predicted by the diametric model, are due to hypomentalism (in autism) or hypermentalism (in psychosis) is not directly discernable in the Director task. Critically, however, the fact that our data show that highly psychosis prone individuals err at similar levels to individuals with high autistic tendencies is not inconsistent with the diametric model. Both hypomentalism and hypermentalism can equally lead to deleterious effects on mentalizing abilities, albeit for different reasons, because otherwise they could not explain the fact that both disorders result in impaired social ability. With this

in mind, hypermentalizing is a plausible cause of errors, and it provides a way of making sense of how psychosis proneness (leading to hypermentalizing) can compensate for autistic tendencies (which could lead to hypomentalizing) (Abu-Akel & Bailey, 2000; Ciaramidaro et al., 2014). We speculate that, under time pressure, mentalizing places high demands on information selection whereby overly narrow information selection can lead to undermentalizing whereas overly broad selection can lead to overmentalizing. Consequently the efficiency of information flow and the frequency with which information is captured has an effect on the number of hypotheses generated and consequently the probability assigned to each hypothesis (Thomas, Dougherty, & Buttaccio, 2014). Information capture tends to be slow in autism due to increased focus of attention (Baron-Cohen et al., 2001; Russell-Smith et al., 2010), and fast in individuals with positive schizotypy/schizophrenia due to overswitching (Yogev, Sirota, Gutman, & Hadar, 2004). Thus by considering the mechanisms behind mentalizing, it becomes apparent how these different mentalizing styles, characteristic of autism and schizophrenia, can compensate for one another. Another important difference between both conditions is that schizophrenia is characterized by a 'jumping to conclusions' cognitive style (which appears to be specifically associated with delusions), whereas autism is characterized by a more deliberative cognitive style (Brosnan, Chapman, & Ashwin, 2014). The attenuating effect, observed in individuals presenting with high expressions in both autism and psychosis traits (Figure 2.3), thus predicts the presence of a brain mechanism that can accommodate the co-existence of these contrasting cognitive styles. The anti-correlational nature of the default mode network (associated with mentalistic thinking) with the task positive network (associated with mechanistic thinking) (Jack et al., 2012) is a promising neural framework to investigating these contrasting mentalizing styles in autism and schizophrenia.

Substantial evidence has accumulated showing that psychosis and autism traits are not bound to the presence of the disorder (Baron-Cohen et al., 2001; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009), with clinical and non-clinical forms of these traits share common genetic, neurocognitive, and neurobiological features (Corlett & Fletcher, 2012; Lustenberger et al., 2014; Noguchi, Hori, & Kunugi, 2008; Stefansson et al., 2014; Vollema, Sitskoorn, Appels, & Kahn, 2002), so with due caution (David, 2010), we consider the clinical relevance of the current approach and findings. First, in the search for disorder-specific phenotypic markers it is difficult to distinguish whether the aberrant marker is a cause or consequence of the disorder. By showing that the presence of sub-threshold clinical traits in healthy adults impact functions that are deficient in patients with these disorders, we provide evidence for a mechanism by which the risk of the disorder may, at least in part, be mediated through variation in these socio-cognitive functions. Second, our findings highlight the importance of testing whether social-cognition is moderated by the relative expression of autism versus psychosis within the clinical population. Such confirmation would warrant reconsideration of current practices perceiving these conditions as distinct, and consequently would facilitate the development of individualized mentalizing-based therapeutic approaches (Allen & Fonagy, 2006). Finally, the diametric influences of autism and psychosis traits on behavior, suggest that these conditions are affected by reciprocal causes. Indeed, some phenomena are risk factors for autism but protect against schizophrenia, or vice versa. For example, duplications of 22q11.2 protect against schizophrenia but represent an autism risk factor (Rees et al., 2014), and congenital blindness causes autism traits but protects against schizophrenia (Hobson & Bishop, 2003; Silverstein, Wang, & Keane, 2012). This means that the causes of one condition might be developed into treatments for the other. As has already been pointed out by others (Crespi et al., 2010b), independent efforts demonstrate the potential of this suggestion. For example, mGluR5

antagonists carry a great potential for the treatment of fragile X of which about 30% have comorbid ASD (Dolen & Bear, 2009), and its agonists are being developed for the treatment of schizophrenia (Conn, Lindsley, & Jones, 2009).

Our study is the first to observe that co-occurring autistic and psychotic traits can exert opposing influences on socio-cognitive performance. Reminiscent of the 'normality effect' that is observed in certain co-occurring diametrical pathologies such as Parkinson's disease and hemiballismus (Bergman, Wichmann, & DeLong, 1990; Mitchell, Sambrook, & Crossman, 1985), our findings thus raise the possibility that autism-schizophrenia comorbidity can have an attenuating effect on socio-cognitive difficulties. More broadly, this suggests that some individuals may, to some extent, be buffered against developing either illnesses or present fewer symptoms due to a balanced expression of autistic and psychosis liability, and will only be diagnosed at the extreme state of either illness. In this regard, our analytical approach of indexing these factors in terms of bias and additive effects is potentially a useful framework to understanding the effect of common risk factors.

CHAPTER 3

PERSPECTIVE-TAKING IN INDIVIDUALS WITH BALANCED LOW VERSUS BALANCED HIGH EXPRESSIONS OF AUTISM AND PSYCHOSIS: AN EYE-TRACKING STUDY[4]

[4] This chapter is currently in preparation for submission: Abu-Akel, A., Wang, J., Wood, S.J., Hansen, P.C., Apperly, I.A. (in prep.). Perspective-Taking abilities in individuals with balanced low versus balanced high expressions of autism and psychosis traits: An eye-tracking study. Manuscript in preparation.

ABSTRACT

The expression of autism and psychosis can coexist in the same individual, albeit to varying degrees. It has been shown that this variation can predict performance on one's ability to take the perspective of others, an ability also known as mentalizing. In Chapter 2, we demonstrated that autism and psychosis interactively reduced the likelihood of committing perspective-taking errors. Intriguingly, there was no difference in performance among individuals with balanced expression. In this study, we sought to replicate the findings of from Chapter 2 (in terms of response time) and to investigate possible differences between individuals with low balanced versus high balanced expressions of autism and psychosis while systematically tracking their eyemovements when performing a more sensitive perspective-taking task. The current study replicated the interactive effect observed in Chapter 2 and further revealed that while both the low and high balanced expression groups were equally accurate on the task, the high balanced groups performed at increasing cost. We discuss possible explanations that may account for the discrepancy between the low and high balanced groups.

INTRODUCTION

In Chapter 2, we examined the concurrent effect of autism tendencies and psychosis proneness in healthy adults on perspective-taking abilities. The results revealed that perspective-taking errors are associated with the relative expression of autism versus psychosis following a U-shaped pattern (see Figure 2.3, Chapter 2). However, the high error rates rendered the response time of correct responses unreliable as they were the average of only few data points[5]. Therefore, the first goal of this study was to replicate our findings from

[5] In Chapter 2, there were 8 relational trials, and the average error rate was about 40%. This means that response time data were comprised of only 4-5 data points. This insufficient number of data points renders the response time unreliable for statistical inferences due to the risk of inflated variance (Wang, Ali, Frisson, & Apperly, in press).

Chapter 2 in terms of response time. In addition, the U-shaped pattern of results suggests that a population can be classified into four distinct groups who vary in terms of their expression of autism and psychosis. Namely, the population can be classified into an autism-dominant group, a psychosis-dominant group, a balanced low expressions group, and a balanced high expressions group. As expected, the dominant groups were more likely to make perspective-taking errors. Intriguingly, however, individuals with high balanced expressions of autism and psychosis (henceforth, the HAHP group) performed better than the dominant groups, and just as well as the low balanced group (henceforth, the LALP group). We ask whether the LALP and HAHP groups are indeed similar? This is an important question, as the equifinality in performance for both the LALP and HAHP in terms of their probability of making errors, does not necessarily imply that decisions were made using similar strategies or patterns of information processing. To address these two goals, we employ in this study a more sensitive version of the director task ((Wang et al., 2015); see Methods) that allows us to examine response times as well as possible information processing differences between the balanced groups by systematically tracking their eye-movements.

The task in this experiment was modified in the following important respects. First, given our interest in response time, we followed a different instruction protocol with the purpose of increasing accuracy. To do so, we followed the "two-step" instruction protocol, which has been shown to significantly reduce perspective-taking errors (Wang et al., 2015). According to this protocol, in the first step, participants, as in the original task, are first made aware of perspective differences vis-à-vis the director, and that they need to take this perspectival difference into account when fulfilling the director's instructions. In the second step, participants are also shown how perspectival difference can lead to egocentric errors. Specifically, participants are told the following: "for example, if she asks you to *nudge the small ball one slot up*, she cannot be talking about this object (experimenter points to the

smallest ball from the participant's perspective—marked Y in Left Panel of Figure 3.1 below) because this object is not available to her. Instead, she must be talking about this object (experimenter points to the smallest ball from her perspective in the open slot—marked X in Left Panel of Figure 3.1)."

Figure 3.1. (Left Panel) Experimental condition of the relational trial. This condition contains a distractor marked Y. (Right Panel) Control condition of the relational trial. In this condition, the distractor from the experimental condition is replaced with an irrelevant item, a "juice carton".

Second, all experimental trials in this version of the task are of the relational type. The inclusion of relational-only instructions is based on the results from Chapter 2 suggesting that relational instructions are more sensitive to inter-individual differences in autism tendencies and psychosis proneness than the ambiguous instructions. For example, in response to the director's instruction to "*nudge the small ball one slot up*", the participant needs to choose from three balls (i.e., a small, a medium and a large ball) the appropriate referent, from the director's perspective. This is done by suppressing or ignoring the smallest ball from the participant's perspective (i.e., the distractor object, Marked Y in Left Panel of Figure 3.1) because the director cannot see it and is not aware of its existence.

Third, eye-movements patterns were recorded along the time course of each trial. This methodology allowed us to track participants' pattern of information processing in terms of

both time and number of fixations on specific areas of interest within the display. Specifically, each trial was segmented into three phases: an *inspection phase,* a *lead-in phase,* and an *integration phase.* The *inspection phase* referred to the 5 s study time of the grid, before the instructions were spoken. During this phase, and on the assumption that participants show preference to common ground objects (i.e., those available to both the participant and the director) than to privileged ground objects (those only available to the participant) (Barr, 2008; Heller, Grodner, & Tanenhaus, 2008), participants were expected to dwell and fixate more on common ground objects. The *lead-in phase* lasted for 913.52 ms and referred to the time it took to utter the first two words of the instruction, i.e., "*Nudge the*". The separation of this phase from the inspection phase is justified on the assumption that the onset of the director's voice may guide participants to clearer anticipation of the object they would be required to move. During this phase, no information was yet given to the participant regarding the specific object the director wanted to move, and so participants were similarly expected to dwell and fixate more on common ground objects. Such bias to common ground objects in both the inspection and lead-in phases might reflect the participant's anticipation that the director would ask to move an object from the shared common ground. Finally, the *integration phase* referred to the time elapsed from the onset of the adjective "*...small ...*" until the selection of the target. The utterance of the adjective marks the start of the integration phase since it is the earliest point when participants can resolve the reference. During this phase, we predicted differences in the time required to make the selection in the control versus the experimental trials. In the experimental trials, time was expected to be longer due to the expected interference from the distractor object whilst resolving the identity of the referent. Control trials did not contain distractor objects. Given that distractor objects could influence processing time and target selection, we also examined proportion of trials containing fixations on the distractor.

By using the two-step protocol, we predicted that participants would overall obtain high level of accuracy on this task. However, we predicted that participants would nonetheless be slower and not as accurate in the experimental compared to the control condition. Previous studies have shown that response times remain sensitive to the cost associated with holding in mind another's perspective, even when participants made very few errors (Samson, Apperly, Braithwaite, Andrews, & Bodley Scott, 2010; Surtees, Butterfill, & Apperly, 2012; Wang et al., 2015). We also predicted that autism tendencies and psychosis proneness would interactively modulate response time, thus replicating the effect we observed in Chapter 2, albeit for error rates. We did not have a priori hypothesis about the effect of inter-individual differences in autism tendencies and psychosis proneness on the eye-tracking measures, except for latency to final target fixation. During latency to final target fixation, people tend to fixate on an object prior to selection, and hence this period has been regarded as the decision time (Wu & Keysar, 2007). As latency to final target fixation might be viewed as a measure of the time taken to resolve reference, we predicted an interactive effect for autism and psychosis during this time window, which is potentially more sensitive than response times. This aspect of the analysis for the remaining eye-tracking measures will be exploratory in nature. With respect to group differences, while we do not expect the LALP and the HAHP group to differ in their accuracy, we predict that the HAHP will exhibit a greater processing cost. This is based on the assumption put forward in Chapter 2 suggesting that individuals in the HAHP group arrive at their answers through compensatory mechanisms, and thus they are likely to come at some cost. It is important to note, that this specific hypothesis motivated the comparison of these groups independent of the others.

METHODS AND MATERIALS

Participants

A total of 100 healthy adults, recruited through the University of Birmingham Research Participation Scheme (RPS), participated in this study for a course credit. Given our focus on the low and high balanced groups, we also contacted participants from the original experiment who scored above the median splits of both the Autism Quotient Spectrum (AQ) (Baron-Cohen et al., 2001) and the positive scale of the Community Assessment of Psychic Experiences (CAPEp) (Stefanis et al., 2002). As in Chapter 2, the assessment of positive schizotypy rather than the general construct of schizotypy is based on evidence for autism-positive schizotypy axis in the non-clinical population (Dinsdale et al., 2013), and that negative symptoms do not reliably discriminate between the ASD and SSD (Spek & Wouters, 2010). Four participants were recruited through this call. Participants self-reported that they have no history of psychiatric illness, epilepsy, neurological disorders, or brain injury, current or past alcohol and/or substance abuse problems. However, data of two participants were lost due to program failure, and 1 for failing calibration of eye-movements. Thus the final sample consisted of 97 participants. The study was approved by the University of Birmingham Research Ethics Committee, and written informed consent was obtained from all participants.

From this pool of participants we identified participants with low and high balanced expressions of the AQ and CAPEp scales. This was done by first dividing the overall sample into low and high AQ scorers using a median split, and similarly into low and high scorers on the CAPEp. Using these initial classifications, we formed the two balanced groups, i.e., the Low Autism Low Psychosis (LALP) and the High Autism High Psychosis (HAHP) groups as shown in Figure 3.2 below. Table 3.1 summarizes the characteristics of the overall sample and the balanced groups.

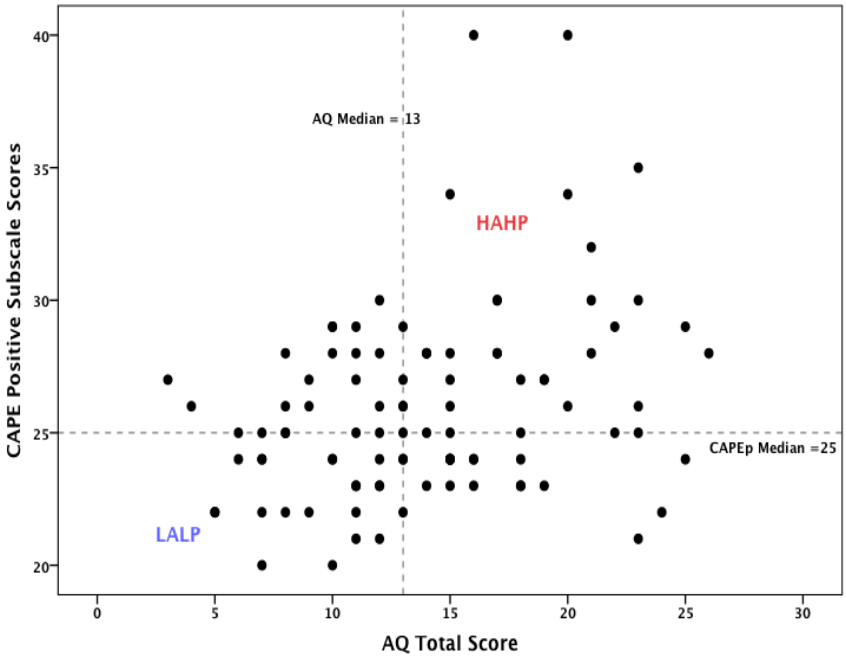

Figure 3.2. Classification of the sample based on median splits of the AQ and CAPE positive subscale (CAPEp) scores: The dotted lines represent the median splits for the AQ and CAPEp scales. LALP=Low Autism, Low Psychosis. HAHP=High Autism, High Psychosis.

Table 3.1. Characteristics of overall sample and the low and high balanced groups

Variable	Sample (N=97)	LALP (N=30)	HAHP (N=26)	Group Differences
Gender (M, F)	17, 80	5, 25	5, 21	χ^2= 0.06, p=.80
Age	19.34±0.83	19.33±0.88	19.73±2.41	t=-.84, df=54, p=.40
AQ	13.91±5.27	9.57±2.60	18.96±3.45	t=-11.61, df=54, p<.001
CAPEp	25.96±3.70	23.17±1.53	29.81±3.87	t=-8.66, df=54, p<.001

LALP = Low autism low psychosis; HAHP = High autism and high psychosis; AQ = Autism Quotient; CAPEp = Community Assessment of Psychic Experiences, positive subscale.

Procedure

In a quiet room, participants first completed the modified version of the perspective-taking task while recording their eye-movements. Participants then completed the CAPEp and the AQ questionnaires.

Materials

Questionnaires

The AQ and the CAPEp scales have been described in Chapter 2. In this study, the internal consistency of the CAPEp (Cronbach's $\alpha = .70$) and the AQ (Cronbach's $\alpha = .72$) is good. The scores on the scales correlated modestly (r_ρ=.29, p=.003).

The Perspective-Taking Task

In this study, we utilized a modified version of the perspective-taking task described in Chapter 2. Specifically, the instruction protocol of the current task highlighted (1) perspective differences between the participant and the director, and the need to take this perspectival difference into account when fulfilling the director's instructions to move objects about the grid, and (2) showed the participant an example demonstrating how such perspectival difference can lead to egocentric errors as described above.

As in the original experiment, there were a total of 128 instructions given in 4 blocks of 32 instructions each. During each block, there were 8 grids, and during each grid the director gave 3-5 instructions, of which one was a critical (control or experimental) instruction. In this version of the task, all the 32 critical instructions were of the relational type (see example experimental and control trials in Figure 3.1). Once the instruction is played, the participant has 4 s to respond. If a selection is not made during this time, the next instruction is played or a new grid is presented. Objects were moved by clicking on it with the computer mouse and dragging it to the nearby slot, up/down or left/right, as instructed. It is important to note that whilst the 128 instructions were matched for the number of up/down, left/right instructions, the critical trials only contained up/down instructions to reduce potential noise from left/right confusion.

Eye-movements record

Participants' eye-movements was recorded at 1000Hz with an Eyelink 1000 (SR Research). Participants were positioned on a chin rest 60cm from a 24 inch gaming computer screen. The grid-images subtended 26.93° (width) by 20.15° (height). We drew interest areas around each slot on the grid, which subtended 3.25° (width) by 3.15° (height). A 13-point calibration was carried out before each block. After the end of each block, participants were encouraged to take a break to avoid neck strain and fatiguing of the eyes.

Eye-movements data, in both the control and experimental conditions, are reported for three phases of a trial in which the participant made correct responses, i.e., during the *inspection, lead-in* and *integration* phases. Within the inspection and lead-in phases, we calculated, for both the control and experimental conditions, the average time a participant dwelled on common ground objects (those available to both the participant and the director) versus privileged ground objects (those only available to the participant). Since the number of common and privileged ground objects was uneven for most grids, the dwell time is thus confounded by the number of objects available in each ground. To adjust for this, the average dwell time for both the common and privileged ground objects was calculated by dividing the cumulative dwell time by the number of objects available in each ground. However, given that during both the inspection and lead-in phases the participants are unaware whether they will need to take the director's perspective, and that the control and experimental girds differed by only one object, the data of the average dwell time were collapsed across the control and experimental conditions for both phases. Similarly, we also calculated the average number of fixations landed on both the common and privileged ground objects, while adjusting for the number of items in the common and privileged grounds.

During the integration phase, we calculated, in both the control and experimental conditions, the average amount of time elapsed from the onset of the adjective until the final

fixation on the target selected for response. This is termed *latency to final target fixation*. Unlike the inspection and lead-in phases, in this phase it is important to make the distinction between the control and experimental conditions, as we anticipate an effect on the processing time required to resolve the reference in the presence of a distractor object (i.e., the small ball marked Y in Left Panel of Figure 3.1).

In addition, during the integration phase we also computed the proportion of trials during which the participants fixated on the distractor item in the grid at least once during the experimental trials. This was to assess the degree to which the participants were distracted by the competing item available to them in the privileged ground whilst they were trying to resolve the item referred to by the director.

RESULTS

Overall Sample: Behavioral data

First, we report the behavioral data in terms of accuracy and response time of accurate responses for the entire sample (see Table 3.2). Participants overall were more accurate ($t_{df=96}$=3.64, p<.001, Cohen's *d*= .47) and faster ($t_{df=96}$=-3.66, p<.001, Cohen's *d*= .25) on the control compared to the experimental trials. Accuracy scores were negatively correlated with response times on both the control (r_ρ=-.31, p=.002) and experimental (r_ρ=-.33, p=.001) conditions, suggesting that there is no tradeoff between accuracy and response times.

Table 3.2. Sample overall performance in terms of accuracy (proportion correct) and response time

	Mean Accuracy (Proportion ± SD)		Mean Response Time (ms ± SD)	
	Control	Experimental	Control	Experimental
Sample (N=97)	0.97±0.06	0.91±0.17	2932.54±178.47	2980.92±213.04

Overall sample: Eye-movements record

A series of paired-samples t-tests investigated the participants' eye-movements pattern in terms of average dwell time per object as well as the average number of fixations on common versus privileged ground objects in both the inspection and lead-in phases. We also examined differences in latency to final target fixation during the integration phase in the control versus the experimental trials (see Table 3.3). The analysis revealed that participants overall dwelled more on common ground objects during both the inspection ($t_{df=96}$=2.26, p=.026, Cohen's *d*= .29) and lead-in phases ($t_{df=96}$=2.37, p=.020, Cohen's *d*= .31). They also fixated on common more often than privileged ground objects during both the inspection ($t_{df=96}$=2.69, p=.008, Cohen's *d*= .26) and lead-in phases ($t_{df=96}$=2.57, p=.012, Cohen's *d*= .32). During the integration phase, latencies were longer in the experimental than the control condition at a trend level ($t_{df=96}$=-1.81, p=.074, Cohen's *d*= .18).

Table 3.3. Summary of eye-movement record in the inspection, lead-in and integration phases of a trial for the entire sample (N=97). Standard errors in parentheses

	Inspection Phase		Lead-in Phase		Integration phase	
	Common Ground	Privileged Ground	Common Ground	Privileged Ground	Control trials	Experimental trials
Dwell time per object (ms)[1]	345.28 (8.48)	321.98 (8.05)	78.22 (2.35)	70.93 (2.38)		
Average fixations per object[2]	1.33 (0.03)	1.24 (.04)	0.27 (0.01)	0.25 (0.01)		
Latency to final target fixation (ms)					2289.83 (27.51)	2354.61 (42.72)

[1] Only fixations over 100ms were included, as saccades typically take from 30-120ms (Young & Sheena, 1975).

[2] The first 200ms of the inspection phase were excluded from the dwell-time analysis, as there is typically a 100-200 refractory period before a saccade is made (Young & Sheena, 1975).

In addition, participants, on average, fixated on the distractor object in 59% of the experimental trials (95% CI = 54.74, 63.22); the control condition contained no distractor.

Individual differences as a function of AQ, CAPEp and their interaction: Response time

To examine the effect of autism and psychosis scores and their interaction on the accuracy and response times during the control and experimental conditions, we conducted regression analyses using generalized linear models. The omnibus tests were nonsignificant for accuracy in both the control (χ^2 =5.85, df=3, p=.119) and experimental ($\chi^{=2}$ .20, df=3, p=.98) conditions, as well as for response time in the control condition (χ^2 =5.97, df=3, p=.113). However, the omnibus test for response times during the experimental condition was significant (χ^2 =7.95, df=3, p=.047). As shown in Table 3.4, the model's parameter estimates (i.e., the main effects and the interaction term) are all significant.

Table 3.4. Summary of coefficients with response time on the experimental relational trials as the dependent variable

Model / Coefficient	β	(SE)	Waldχ^2	df	Sig.
Constant	1645.58	523.36	9.89	1	=.002
AQ	73.96	31.39	5.55	1	=.018
CAPEp	50.10	20.75	5.83	1	=.016
AQxCAPEp	-2.71	1.22	4.95	1	=.026

AQ = Autism Quotient; CAPEp = Positive scale of the Community Assessment of Psychic Experiences.

The results suggest that autism and psychosis scores interactively reduce response time. We unpacked the interaction following the method by Hayes and Matthes (Hayes & Matthes, 2009) as described in Chapter 2. As shown in Figure 3.3A, the increase in response time as a function of AQ scores depends on the level of psychosis proneness and is particularly attenuated in individuals with high psychosis scores (defined as 1 SD above the mean). Similarly, Figure 3.3B shows that the increase in response time as a function of psychosis

depends on the level of autism tendencies and is particularly attenuated in individuals with high AQ scores (defined as 1 SD above the mean).

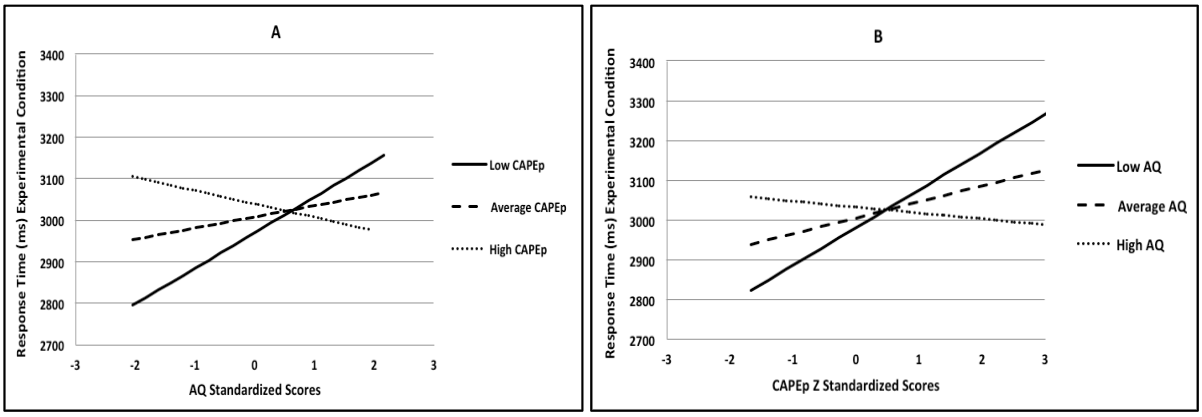

Figure 3.3. (A) The relationship between autism tendencies and response time, evaluated at low (Mean – 1 SD), average, and high CAPEp scores (Mean +1 SD). (B) The relationship between psychosis proneness and response time, evaluated at low (Mean – 1 SD), average, and high AQ scores (Mean +1 SD).

Individual differences as a function of AQ, CAPEp and their interaction: Eye-movements record

Using generalized linear models, we examined the association of autism, psychosis and their interaction as a function of the average dwell time and average number of fixations during both the inspection and lead-in times on the common and privileged ground objects. We also examined the association of these parameters with latency to last target fixation during the control and the experimental trials, and with the proportion of trials during which the participants fixated on the distractor during the experimental trials. None of the ombibus tests were significant (all *ps*>.16).

Group analysis: Behavioral data

To examine differences between the balanced groups in their performance on the task, we conducted two separate, 2x2 ANOVAs of condition (experimental vs control) x group (LALP, HAHP) for accuracy and response time. For accuracy, the analysis revealed only a

main effect for condition (F(1,54)=7.69, p=.008, η_p^2=.13), where participants were more accurate in the control (M(SE)=.97(.008)) than the experimental (M(SE)=.90(.028)) condition. For response time, the analysis revealed a main effect for condition (F(1,54)=6.69, p=.012, η_p^2=.11), where participants were faster in the control (M(SE)=2925.69(24.79)) than the experimental (M(SE)=2968.08 (29.20)) condition, and a significant condition x group interaction (F(3, 51)=4.72, p=.034, η_p^2=.08) (see Figure 3.4). There was no main effect for group (F(1,54)=1.04, p=.31).

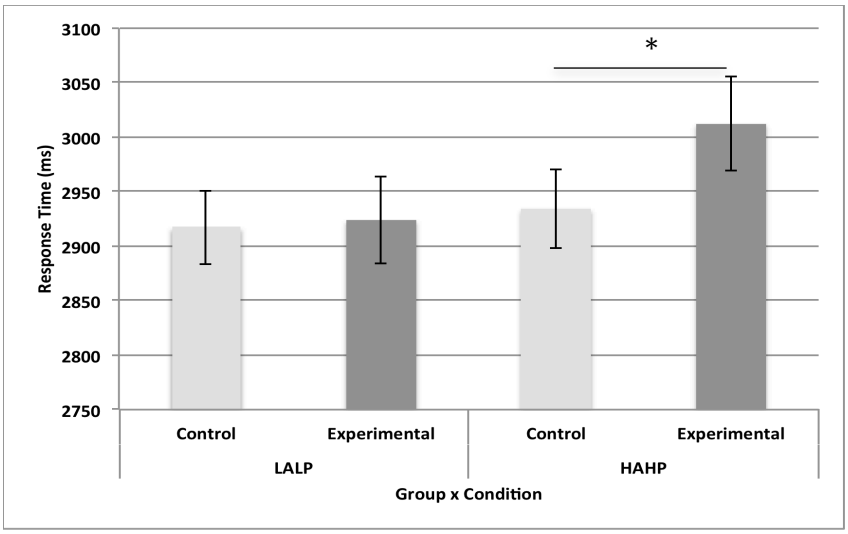

Figure 3.4. Mean response time of the balanced groups in the experimental and control conditions. LALP=Low Autism Low Psychosis, HAHP=High Autism High Psychosis. Error bars represent standard error of the means.

Post-hoc t-tests corrected form multiple comparisons (significant if p<.013) revealed a significant difference only between the control and experimental conditions in the HAHP group with the group being slower in the experimental (M(SE)=3012.16(42.75)) than the control (M(SE)=2934.16(36.29) condition ($t_{df=25}$=-2.90, p=.008, Cohen's *d*= .45).

Group analysis: Eye-movements record

Inspection phase: Dwell time and fixations on privileged vs common ground objects

For both the dwell time and number of fixations during the inspection phase, the ground

(common vs privileged) x group (LALP, HAHP) ANOVAs revealed only a main effect for ground. Specifically, participants dwelled significantly more on the common (M(SE)=347.82(10.84) versus the privileged (M(SE)=313.23(11.25) ground objects (F(1,54)=7.18, p=.010, η_p^2=.12). They also fixated significantly more frequently on the common (M(SE)=1.37(0.44) versus the privileged (M(SE)=1.24(0.05) ground objects (F(1,54)=9.29, p=.004, η_p^2=.15).

Lead-in time phase: Dwell time and fixations on privileged vs common ground objects

For both the dwell time and number of fixations during the lead-in phase, the ground (common vs privileged) x group (LALP, HAHP) ANOVAs revealed only a main effect for ground. Specifically, participants dwelled significantly more on the common (M(SE)=79.01(3.08) versus the privileged (M(SE)=69.91(3.32) ground objects (F(1,54)=5.42, p=.025, η_p^2=.09). They also fixated significantly more on the common (M(SE)=.27(0.01) versus the privileged (M(SE)=.24(0.01) ground objects (F(1,54)=4.45, p=.040, η_p^2=.08).

Integration phase: Latency to final target fixation

To examine differences in the average latency to last target fixation, we conducted a condition (control vs experimental) x group (LALP, HAHP) ANOVA. The analysis revealed a trend for a significant condition x group interaction (F(1,89)=3.04 p=.087, η_p^2=.05) (see Figure 3.5). Exploratory, post-hoc analysis revealed longer latency during the experimental M(SE)=2366.72(61.63) compared to the control M(SE)=2276.78(56.27) condition ($t_{df=25}$=-2.34, p=.028, Cohen's *d*= .30) only in the HAHP group.

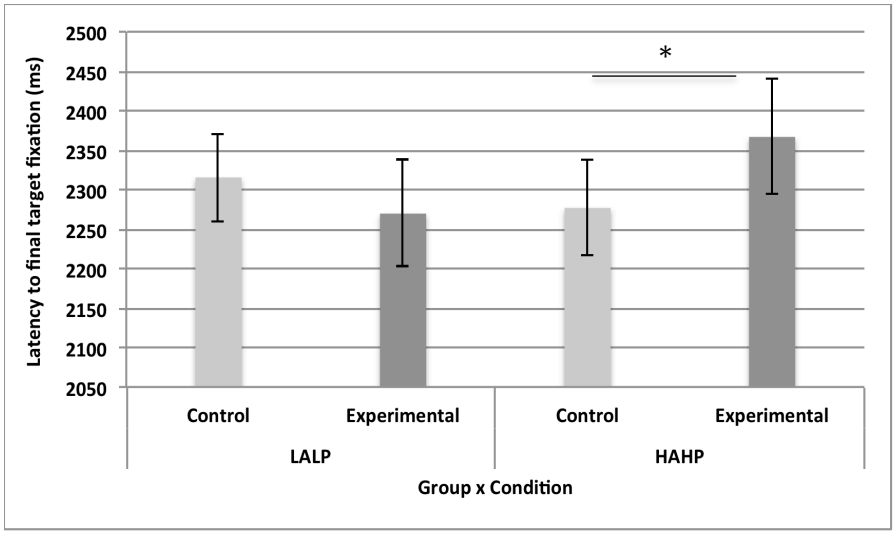

Figure 3.5. Mean latency to last target fixation of the balanced groups in the experimental and control conditions. LALP= Low Autism Low Psychosis; HAHP= High Autism High Psychosis. Error bars represent standard error of the means.

Proportion of trials containing fixations on distractor

In examining the proportion of trials containing fixations on the distractor, we only analyzed group differences during the experimental condition, as the distractor is only present during this condition. There was no difference between the LALP (M(SE)=.57(.04) and HAHP (M(SE)=.55(.05) groups ($t_{df=54}$=.31, p=.76).

DISCUSSION

The aim of this study was twofold. First, we wanted to replicate the findings from Chapter 2 in terms of response time. Second, we wanted to examine possible differences between the low balanced (LALP) and high balanced (HAHP) groups. To do this, we adopted a more sensitive version of the perspective-taking task that was designed to reduce the error rates thus allowing for the examination of the effects of autism tendencies and psychosis proneness on response times. Our findings show that the two-step instruction method was successful in considerably reducing the error rate. The participants achieved over 90% correct responses, which is in stark in contrast to the 42% error rate we reported in Chapter 2. This is consistent

with previous work using the "two-step" instruction (Wang et al., 2015), and suggests that by demonstrating how the director's perspective can constrain reference, participants are able to achieve high level of accuracy on this task. We also observed an interactive effect between autism and psychosis scores on response time, such that the effect engendered by the expression of one condition was attenuated by the relative expression of the other. This result thus replicates our finding from Chapter 2, in a largely independent sample from the sample reported in Chapter 2. It should be noted, however, that this is based upon observing the effect in the experimental trials, and not on demonstrating a difference between the patterns of experimental and control trials.

With respect to differences between the LALP and HAHP groups, our results indicate that while both groups were equally efficient and accurate on the task, the participants from HAHP were slower in the experimental compared to the control condition. The delayed response time in the experimental condition may reflect greater egocentric interference, and thus the need for more time to resolve the identity of the referent. This effect is somewhat captured during the integration phase of the trial as suggested by the slower latency to final target fixation times. Thus, the difficulty of the HAHP group appears to occur during the phase that requires them to integrate incoming linguistic instruction with the available ground information. It is noteworthy that this difficulty is unlikely to have resulted from how ground information was processed, as both groups showed preference to common ground objects, suggesting that both groups equally anticipated the referent to come from common ground objects. Similarly, the lack of difference between the groups in the proportion of trials containing fixations on the distractor suggests that the processing of the distractor object is equally unlikely to account for the egocentric effect observed for the HAHP group during the experimental condition. However, with respect to the latter suggestion, although the likelihood of looking at the distractor on a given trial did not differ between the LALP and

HAHP groups, the fact that interference occurred only during the experimental condition, the greater cost suffered by the HAHP group may be due to greater difficulty disengaging from the distractor object.

If the integration of linguistic and ground information during the experimental condition is responsible for retarding perspective-taking efficiency in the HAHP group, it is conceivable that the difference between the groups lies in executive functioning. Indeed, prior work has shown that executive functioning can influence performance on perspective-taking tasks (Brown-Schmidt, 2009). In the context of our task, it is possible that holding in working memory another potential referent (i.e., discerning between two relevant referents vs three referents) is a potential source for the processing delay in the experimental condition. It is important to note that information complexity is unlikely to affect perspective taking per se (i.e., competence), but only the efficiency in doing so (i.e., performance). Experimental manipulations that increase or reduce the number of potential referents can be instrumental in testing this hypothesis. For example, by adding another ball to the three available balls that the participant needs to choose from when asked to "*nudge the smallest ball one slot up*" we should observe longer latencies in identifying the correct reference. Alternatively, we can assess this hypothesis by assessing the performance of the HAHP group in terms of inter-individual differences in working memory capacity. This is plausible, as previous work has shown that working memory capacity can lead to longer latencies during the integration phase of the director task (Lin, Keysar, & Epley, 2010).

In conclusion, the present study successfully replicated the interactive effect of autism and psychosis on perspective-taking, using response times as an outcome measure. This finding underscores the robustness of this effect and thus the need for the simultaneousness assessment of autism and psychosis when examining socio-cognitive abilities. In addition, the response time data were sensitive in discerning differences between the LALP and HAHP

groups. While our previous findings, from Chapter 2, in terms of error rate lead us to believe that the groups were equifinal in their performance, the eye-tracking data suggest that both groups differ in their ability to integrate pertinent linguistic input with available ground information. While this difference is subtle, it constitutes, nonetheless, the first evidence suggesting that the HAHP group resolves perspective-taking conflicts less efficiently than the LALP group. Further research is needed to understand in greater detail the source of this interference and more specifically how and what information is processed en route to resolving conflicts emanating from perspectival difference.

CHAPTER 4

AUTISM TENDENCIES AND PSYCHOSIS PRONENESS INTERACTIVELY MODULATE SALIENCY COST[6]

[6] This chapter is currently under review: Abu-Akel, A., Apperly, I.A., Wood, S.J., Hansen, P.C., Mevorach, C. Autism tendencies and psychosis proneness interactively modulate saliency cost.

ABSTRACT

Saliency is a candidate endophenotype for both autism and psychosis spectrum disorders. However, while both conditions are associated with saliency-related deficits, there is evidence that autism can render some benefits on some tasks. Recent evidence suggests that autism and psychosis can co-occur at both the diagnostic and trait levels. In this study, we investigated saliency-based selection in a large cohort of neurotypical adults in whom both autism and psychosis traits have been assessed. Converging evidence from two experiments suggest that autism tendencies and psychosis proneness interactively modulate the cost incurred in the presence of a task-irrelevant salient distractor, such that the effect engendered by the expression of one condition depends on the co-occurring expression level of the other condition.

INTRODUCTION

In both clinical and non-clinical participants, traits for autism and schizophrenia spectrum disorders (ASD and SSD, respectively) are associated with differences in attentional processing. Although these are often seen as deficits, there is also some evidence of autism giving benefits on some tasks. As such, it is far from clear whether autism and psychosis traits yield these effects for the same reasons, not least because it is uncommon for these traits to be assessed in the same participants. Recent theoretical and empirical evidence, however, highlights the need to assess autism and psychosis traits in tandem as they might be additive or even interact (Abu-Akel, Wood, Hansen, & Apperly, 2015). Here, we investigate the interactive effect of autism and psychosis traits on saliency-based selection in a large cohort of neurotypical adults. Salience-based selection is a key attentional mechanism associated with the ability to bias attention towards (or away from) salient information (Mevorach et al., 2006), and is considered a candidate endophenotype for both autism (Uddin

et al., 2013) and schizophrenia (Kapur, 2003). As such understanding how healthy variations in these traits impact attentional processing can facilitate our understanding of clinical autism and psychosis and their interaction.

Research in SSD and the broader spectrum of these traits in healthy participants has consistently and robustly shown increased processing cost in the presence of salient distractor stimuli (Ettinger et al., 2015; Hahn et al., 2010; Minas & Park, 2007; Poirel et al., 2010). For example, in a global-local processing paradgim where participants were required to judge whether a pair of compound stimuli (global froms composed of local forms) were identical or not, there was a significant slowing in information processing in schizophrenia patients, particularly in the presnece of a salient distractor element at the local level (Poirel et al., 2010). Similarly, neurotypicals with high positive schizotypy scores had more difficulties filtering out non-relevant salient stimuli (the more complex figure) while they were required to detect an embedded figure (Russell-Smith et al., 2010).

Research in ASD and the broader spectrum of ASD traits in neurotypical participants also reports significant effects on information processing in the presence of salient distractors (Becchio et al., 2010; Behrmann et al., 2006; Leader, Loughnane, McMoreland, & Reed, 2009). For example, Becchio et al. (2010) have shown that, compared to typically developing children, children with ASD were significantly slower in identifying objects in the presence of their cast-shadow compared to objects without a shadow. In addition, both individuals with ASD and their unaffected brothers are less efficient than controls at a visual divided-attention task requiring the suppression of spatially intervening distractors, with the unaffected brothers performing intermediately (Belmonte, Gomot, & Baron-Cohen, 2010). While these studies collectively suggest that autism is associated with reduced ability to filter out irrelevant information, there is contrasting evidence suggesting that individuals with ASD are more adept at ignoring distracting salient information. For example, compared to

typically developing children, children with ASD have been shown to be more resistant to both non-social (e.g., odd balls) (Blaser, Eglington, Carter, & Kaldy, 2014) and social (e.g., faces) distractors (Riby et al., 2012), and that the degree of interference by the presence of the distractor appears to negatively correlate with the severity of autism functioning (Riby et al., 2012). Similarly, individuals with ASD show less global precedence (assuming that the global level is typically more salient) when processing global versus local information (Koldewyn, Jiang, Weigelt, & Kanwisher, 2013), although this study also reports that their processing of global information is unimpaired when explicitly instructed to attend to the global level. Although, it is plausible that the inconsistency of findings in ASD might be partly due to unrecognized variation due to other trait dimensions such as SSD, there is significant evidence suggesting that there may be some aspects of saliency processing that are better in ASD.

The evidence described above opens the possibility that traits for ASD and SSD might each have effects on salience processing, and that these effects may interact. While ASD and SSD have been formally conceptualized as distinct disorders since the 1970s (Kolvin, 1971), several recent lines of evidence suggest that there are important cognitive, behavioral, neurophysiological and etiologic relationships between the two disorders (Crespi et al., 2010b; Sasson et al., 2011; P. F. Sullivan et al., 2012). Furthermore, accumulating evidence suggests that the disorders can co-occur at both the diagnostic and trait levels within the individual (Chisholm et al., 2015; Hofvander et al., 2009; Sheitman et al., 2004; Solomon et al., 2011). In the context of such co-occurrence, it is important to determine what the relative impact is of disorder-specific traits on phenotypes within an individual. This question has significant implications for the individual's for treatment and prognosis, as well as the nature of the relationship between ASD and SSD. Despite the recognition of the centrality of saliency-related effects in both ASD and SSD, no previous saliency-related studies have

directly compared both conditions, or the effect of their co-occurrence at either the trait or diagnostic levels.

One approach to evaluating the co-occurring effect of ASD and SSD on the suppression/filtering out of salient information ("saliency" henceforth), is by examining the association of psychosis proneness and autistic tendencies among non-clinical populations. This approach draws on the notion that both autistic (Baron-Cohen et al., 2001) and psychotic tendencies (Allardyce, Suppes, & Van Os, 2007) exist on a continuum, ranging from typicality to disorder, and has the advantage of eliminating the confounding effects of active symptomatology or medication (Stefansson et al., 2014). We therefore investigated the effect of autistic tendencies and psychosis proneness on the cost associated with the processing of information in the presence of competing salient information in a large sample of non-clinical adults. More specifically, we examined how autistic and psychotic tendencies affect the processing of two competing sources of information where one set of information is more prominent (i.e., more readily available for processing) but irrelevant and the other is relevant but is less prominent.

To this end, saliency was examined in two separate experiments. The first is Mevorach et al.'s (2009) variant of the Navon's classic global-local task (Navon, 1977) which assesses overall local and global biases, selective attention and saliency suppression. The second is a novel Face-Scene Perception Task. This task enables us to test for attentional/perceptual biases to socially relevant stimuli (i.e., faces) as well as whether the effects are perceptual or attentional. More specifically, this task enables us to investigate whether the effect of autism tendencies and psychosis proneness is associated with the perception of salient stimuli, or with the suppression/filtering out of competing salient information. The autistic and psychotic tendencies were respectively assessed with the Autism Spectrum Quotient (Baron-Cohen et al., 2001) and the Community Assessment of

Psychic Experiences Questionnaire (Stefanis et al., 2002). These are well-validated questionnaires that have been used extensively to assess these traits in the general population (see Method for details). While the focus of the current study was on saliency, we also tested for the effect of autism and psychosis traits on differences in information processing as a function of level (i.e., local versus global), target (face versus scene) and congruency (congruent versus incongruent information) given research suggesting that information processing related to these factors varies as a function of autism and psychosis (Koldewyn et al., 2013; McCabe et al., 2013; Russell-Smith et al., 2010).

Based on findings from existing literature, we predicted that higher levels of psychosis proneness would increase the burden of information processing in the presence of salient distracting stimuli. While the literature regarding the affect of autism traits is less clear, we further predicted that any increased cost associated with autism tendencies will vary depending on the level of co-occurring psychosis proneness. However, the effect of their co-occurrence on cost depends on the nature of the relationship between autism and psychosis, which as described in Chapter 1 (Figure 1.1) can be independent (or separate), overlapping or diametrical. The independent model predicts that co-occurrence will result in a non-additive effect perhaps due to a ceiling effect, or a dominance effect where the effect is mainly driven by level of psychosis; the overlapping model predicts that co-occurrence will result in an additive effect leading to greater interference by the competing salient distractor; and the diametric model predicts that co-occurrence will result in a sub-additive effect where the cost will be reduced in the presence of both conditions, perhaps through some compensatory effect, whereby saliency suppression is contrastingly modulated by autism and psychosis tendencies. The latter scenario is conceivable if autism, in contrast to psychosis, is less affected by the presence of salient distracting information.

METHODS AND MATERIALS

Participants

Data were collected from 202 healthy adults (43 males, 159 females; mean age = 21.45, SD = 4.33). Participants were university students who participated either for course credit or cash compensation. Participants self-reported that they have no history of psychiatric illness, epilepsy, neurological disorders, or brain injury, current or past alcohol and/or substance abuse problems. The study was approved by the University of Birmingham Research Ethics Committee, and written informed consent was obtained from all participants.

Measures and materials

The Community Assessment of Psychic Experiences (CAPE) Questionnaire

The CAPE questionnaire was used to assess psychosis proneness. This self-report questionnaire is based on the Peters et al. Delusions Inventory-21 (PDI-21) (Peters et al., 1999) and consists of 42 items measuring the presence of *positive* psychotic experiences (20 items), *negative* psychotic experiences (14 items), and *depressive* experiences (8 items) that an individual may have experienced over the last 12 months (Stefanis et al., 2002). The occurrence of these symptoms is reported on a likert frequency scale from 1 (never) to 4 (nearly always). For current purposes, the 20-item CAPE positive scale (CAPEp) is used as a measure of psychosis proneness. The assessment of positive schizotypy rather than the general construct of schizotypy is based on evidence for autism-positive schizotypy axis in the non-clinical population (Dinsdale et al., 2013), and that negative symptoms do not reliably discriminate between the ASD and SSD (Spek & Wouters, 2010). The internal consistency of this scale in this study is very good (Cronbach's $\alpha = .84$), and falls within the range of values reported in other studies within the general population (Lin et al., 2011).

The Autism Spectrum Quotient (AQ) Questionnaire

Autism tendencies were assessed using the AQ. This self-report questionnaire consists of 50 items that measure the presence of traits associated with the autistic spectrum within the general population (Baron-Cohen et al., 2001). Each item is given a score of 0 or 1. The AQ's internal consistency in this study is good (Cronbach's $\alpha = .82$), and is comparable to the values reported in other studies (Austin, 2005).

The Center for Epidemiologic Studies Depression Scale – Revised (CESD-R)

This brief 20-item self-report scale is a revision of the original CESD scale (Radloff, 1977) that closely reflects the DSM-IV criteria for depression (Eaton, Smith, Ybarra, Muntaner, & Tien, 2004). It assesses the individual's level of depressive symptomatology experienced over the last two weeks. A score of zero (not at all or less than one day) to 3 (5-7 days) is given for symptoms experienced over the last week. A score of 4 is given if the individual experiences the symptom nearly every day over the last two weeks. The internal consistency in this study is high (Cronbach's $\alpha = .91$) and is comparable to the values reported in a recent validation study for both a student sample (N=245) and a large community sample (N=6,971) (Van Dam & Earleywine, 2011). Depressive symptoms are measured since they are frequent clinical features in both ASD (Stewart, Barnard, Pearson, Hasan, & O'Brien, 2006) and SSD (Buckley, Miller, Lehrer, & Castle, 2009), and may affect performance on cognitive tasks (Jones, Siegle, Muelly, Haggerty, & Ghinassi, 2010).

The Global- Local Task

In this task, participants were required to identify the global letter of the compound figure made up of small letters (an S or an H) or the local letter of the compound figure (an S or an H) while ignoring information on the other level. As can be seen from Figure 4.1A below,

saliency was manipulated in two ways: Local saliency was achieved by using alternating colors for the local elements (to break grouping), and global saliency was achieved by blurring the local elements. As such, participants were asked to detect the local or the global letter under four conditions: identifying the global letter when the global level is more salient, identifying the global letter when the local level is more salient, identifying the local letter when the local level is more salient, and identifying the local letter when the global level is more salient.

The task consisted of 4 blocks containing 32 trials each for a total of 128 trials equally divided among the 4 different conditions. On half of the trials, the compound figures consisted of the same global and local elements (congruent trials), and on the other half there were different global and local elements (incongruent trials). Each block was preceded with an instruction to either identify the letter at the *local* level or the letter at the *global* level. Participants, seated approximately 60cm from a 17" monitor, were asked to identify the presented letter as quickly and as accurately as possible. Details regarding stimuli's visual angles and positioning on the screen have been described elsewhere (Mevorach, Shalev, Allen, & Humphreys, 2009). Each trial began with a 1500msec fixation cross. Letters appeared against a black background for 150msec, following a 200msec interval (see Figure 4.1B). The next trial began after the participant pressed one of two keys on the keyboard: 'K' and 'M'. 'K' was labeled 'S' and 'M' was labeled 'H'. Key presses recorded the participants' responses and reaction times. The task was presented using Presentation® (Neurobehavioral Systems, www.neurobs.com).

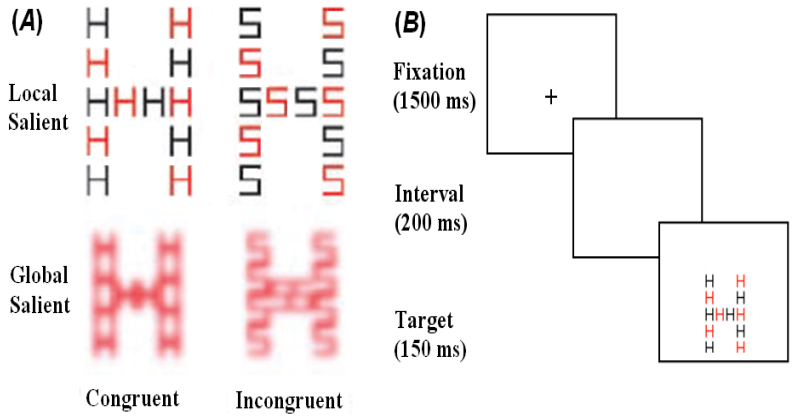

Figure 4.1. (A) Example of stimuli for the global-loca task (Original stimuli were presented against a black background). (B) Typical trial display sequence.

The Face-Scene Perception Task

In this task, participants were required to either detect a face or a scene. There were two faces and two scenes that were associated with two keys on the keyboard: 'K' and 'M'. 'K' was relabeled 'S' and 'M' was relabeled 'H', denoting *Scene* and *Head* respectively). Participants were required to associate the scene or the face with the corresponding letter (H or S). To neutralize memory constraints, a sheet depicting these associations was placed in front of the participant whilst performing the task (see Figure 4.2A). As can be seen from Figure 4.2B, these faces and scenes were superimposed onto each other to manipulate saliency and congruency. In the neutral condition, the face (or the scene) were presented together with a scrambled version of the scene (or the face). The superimposed combinations used a manipulation of the face or scene contrast at a 70%/30% ratio. Thus for more salient face displays, the face was presented at 70% contrast and the scene (or scrambled scene) was presented at 30% contrast. For more salient scene displays, these values were reversed. Congruency and incongruency were achieved by superimposing faces and scenes that were associated with the same letter (i.e., no response conflict) or different letters (i.e., response conflict), respectively.

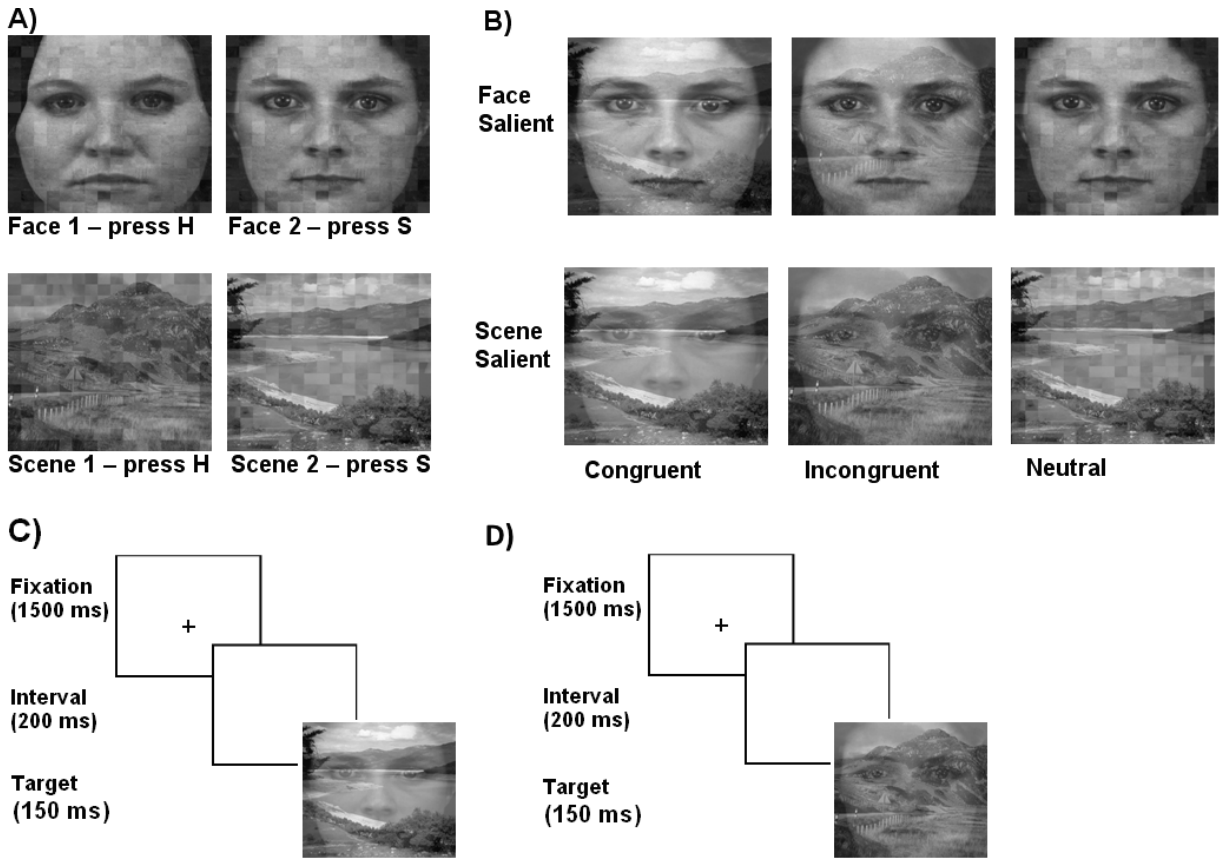

Figure 4.2. (A) Stimuli of the face-scene perception task. (B) Faces and scenes in salient/non-salient, congruent/incongruent and neutral conditions. (C) Typical trial display sequence for congruent stimuli. (D) Typical trial display sequence for incongruent stimuli.

The task consisted of 12 blocks of 12 trials each for a total of 144 trials, equally divided among the congruent, incongruent and neutral conditions. Each block was preceded with an instruction to either identify faces or identify scenes as quickly and as accurately as possible. The instruction remained on the screen for 5 seconds. Each trial then began with a 1500msec fixation cross, and following a 200msec interval, the picture appeared for 150msec (see Figure 4.2C-D for a typical sequence display of congruent and incongruent stimuli). Participants were seated approximately 60cm from a 17" monitor, so that each centimeter on the screen represented ~0.96^{O} of visual angle. The displayed stimuli subtended a visual angle of ~12.82^{O} horizontally and ~12.84^{O} vertically. Key presses recorded the participants'

responses and reaction times. The task was presented using Presentation® (Neurobehavioral Systems, www.neurobs.com).

Procedure

Participants first completed the Global-Local Saliency task (~10min), followed by the Face-Scene Perception task (~20min). This was followed by completing the CAPE and the AQ and the CESD-R in this order (~20min). The entire session lasted about 1 hour.

Analytic approach

Overall performance on the Global-Local task as was assessed using 2x2x2 repeated measures of Level (global vs. local), Saliency (global salient vs. local salient) and Congruency (congruent vs. incongruent). Overall performance on the Face-Scene task was assessed using 2x2x3 repeated measures of Target (Face vs. Scene), saliency (face salient vs. scene salient) and Congruency (congruent vs. incongruent vs. neutral).

Regression analyses using General Linear Models estimated the effect of autism tendencies and psychosis proneness on performance as a function of level (for the Global-Local task)/target (for the face-scene perception task) difference, congruency interference and saliency cost. Saliency cost is the difference in performance between conditions when the target is the salient aspect of the display (Target Salient) and when the target is the less salient aspect of the display (Distractor salient). In the Global-Local task, we calculated the efficiency scores (i.e., RT/proportion correct for each cell of the design for each participant) for level difference (i.e., Global $_{\text{minus}}$ Local), congruency interference (i.e., Incongruent $_{\text{minus}}$ Congruent) and saliency cost (i.e., Distractor Salient (DS) $_{\text{minus}}$ Target Salient (TS)). Similarly, in the Face-Scene Perception task, we calculated the efficiency scores for target difference (i.e., Face $_{\text{minus}}$ Scene), congruency interference (i.e., (Incongruent/ Neutral $_{\text{minus}}$

Congruent/ Neutral)), and saliency cost (i.e., DS $_{minus}$ TS). We also tested the effect of autism tendencies and psychosis proneness on performance in the neutral-only condition to see if they also explain simple effects of perception. The use of efficiency scores allows us to incorporate both RT and accuracy into a single measure (Townsend & Ashby, 1983), and to be consistent with previous studies using similar paradigms (Mevorach, Humphreys, & Shalev, 2006; Mevorach, Shalev, et al., 2009).

The effects of autistic tendencies and psychosis proneness on the simple scores of the participants on these measures were modeled as follows:

(1) Y = i*A + j*P + k*A*P +ε, where A and P are the scores on the AQ and CAPE positive scale, respectively, i, j and k are best fit parameters, and the ε is the error term [Model 1]

Second, the relationship between these measures was expressed in terms of Bias (i.e., the relative dominance of one vis-à-vis the other) and Mean Effect. Thus, the extent that A and P traits are additive one would expect to see a significant Mean Effect, whereas to the extent they are sub-additive/compensatory, one would expect to see a bias effect. To this end, the AQ and CAPEp scores were converted into Z scores which, in turn, were used to calculate the bias and the mean effect scores. This was captured in a model with 5 dependent terms (i.e. two linear, an interaction, and two quadratic terms) as follows:

(2) Y = m*M + n*B + o*M^2 + p*B^2 + q*M*B +ε, where M and B are respectively the mean effect and bias scores, m, n, o, p and q are the best fit parameters, and ε is the error term [Model 2]

While Model 2 is the mathematical derivative of Model 1 (see Appendix 2) it offers two advantages: (1) it can capture both linear and nonlinear trends, and (2) it allows for the

assessment of the nature of the relationship between autism and psychosis in terms of mean and bias effects.

RESULTS

The Global-Local Task

In this task, data were collected from 202 participants. The data of one participant were excluded for a program failure and 5 additional for not following instructions, i.e., detecting global when the task was to detect local and vice versa. Thus the data of 196 participants (41 males, 155 females; mean age = 21.40, SD = 4.36) were included in the analyses for this task. On average, participants scored 27.25(±5.06) on the CAPEp, 16.25(±6.29) on the AQ, and 12.47(±11.13) on the CESD-R. Significant Spearman's ρ correlations were observed between the AQ and CAPEp scores (r=.31, p<.001), the AQ and CESD-R (r=.38, p<.001) as well as between the CESD-R and CAPEp scores (r=.36, p<.001). There were no associations between age and either the AQ or the CAPEp scores (-.07<*rs*<.07, all *ps*>.34). Age was negatively correlated with the CESD-R scores (r=-.16, p=.024). There were no differences between male and female participants on any of these measures except for age where female (M±SD= 20.92±4.08) were younger than the male (M±SD= 23.22±4.93) participants (t=2.76; p=.008).

Figure 4.3 shows the results of participants' performance on the task. The 2x2x2 repeated measure ANOVA reveals a main effect for congruency ($F(1,195)=420.71$, $p<.001$, $\eta_p^2=.68$) where participants were slower in the incongruent (M(SE)=640.96(8.57)) than the congruent (M(SE)=557.39(8.74)) condition. No other main effects were significant. Moreover, the 2-way interactions of level x congruency ($F(1,195)=238.67$, $p<.001$, $\eta_p^2=.55$), level x saliency ($F(1,195)=50.14$, $p<.001$, $\eta_p^2=.21$) and congruency x saliency ($F(1,195)=15.45$, $p<.001$,

η_p^2=.07) were significant, as well as the 3-way interaction of level x saliency x congruency (F(1,195)=64.19, p<.001, η_p^2=.25). Follow-up analyses revealed significant saliency x congruency interactions at both the local (F(1,195)=9.89, p<.001, η_p^2=.05) and global levels (F(1,195)=50.98, p<.001, η_p^2=.21). Furthermore, as can be seen from Figure 3, the shift in salience (from local salient to global salient) when detecting the local letter, or the reverse (from global salient to local salient) when detecting the global letter was associated with increased cost in both the congruent and incongruent conditions (all *ts*>5.6, all *ps*<.001). However, in the congruent condition, the effect of the cost associated with the shift from the local salient to the global salient at the local level (Cohen's *d*=.27) or with the reverse at the global level (Cohen's *d*=.43) was small, although the shift appears more costly at the local (M(SE)=62.45±7.43) than the global level (M(SE)=36.18±6.28) (t=2.69, df=195, p=.008, Cohen's *d*=.28). Conversely, the effects are larger during the incongruent condition when detecting either the local (Cohen's *d*=.56) or the global (Cohen's *d*=.73) letter. However, the shift appears more costly at the global (M(SE)=124.05±13.13) than at the local level (M(SE)=89.12±8.90) (t=2.05, df=195, p=.042, Cohen's *d*=.22). These results replicate the pattern of results observed in earlier studies using this task (Mevorach et al., 2006; Mevorach, Humphreys, & Shalev, 2009), and suggest that the presence of salient distractor has a measurable effect on processing cost.

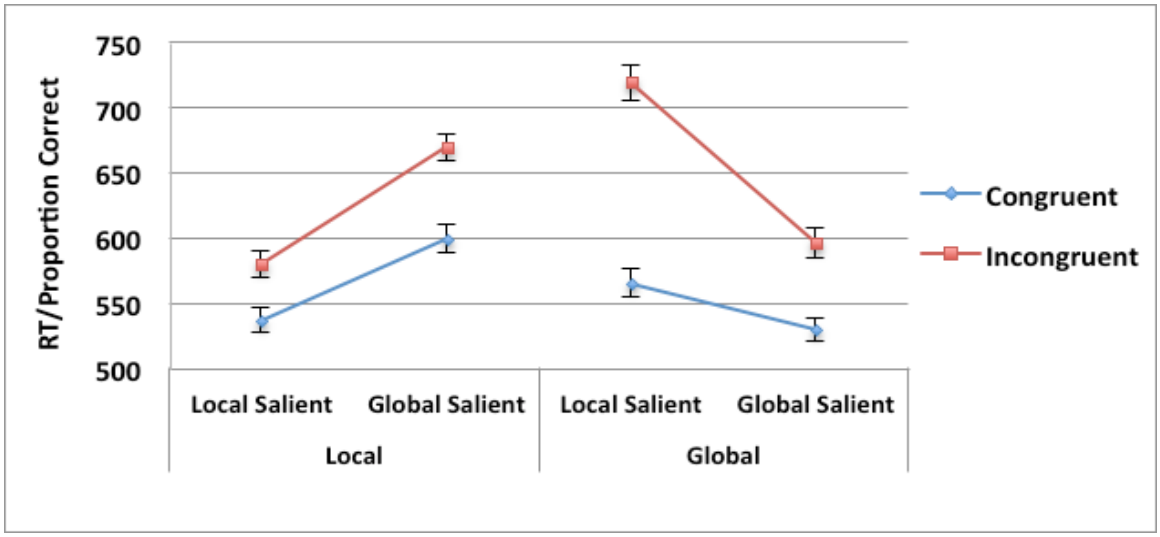

Figure 4.3. Overall performance on the Global-Local Task as a function of level (local vs. global), saliency (local salience vs. global saliency) and congruency (congruent vs. incongruent). Bars represent standard errors.

Estimating the effect of autism tendencies and psychosis proneness on level difference, congruency interference and saliency cost

First, Spearman's ρ indicated that there were no correlations between age or depressive mood on any of the dependent variables (i.e., level difference, congruency interference and saliency cost) except for a negative association between age and congruency interference (r=-.17, p=.015). There were also no significant correlations among the dependent measures, or differences as a function of gender. Each dependent measure was then entered separately into a regression model with the AQ scores, CAPEp scores and their interaction (AQ x CAPEp) as predictors. The model estimating congruency interference was carried out while also controlling for age. The regression models for the level difference ($X^2_{(df=3)}$=2.59, p=.46) and congruency interference ($X^2_{(df=4)}$=3.44, p=.49) were non-significant. The model estimating saliency cost was significant ($X^2_{(df=3)}$, =11.03, p=.012), with parameter estimates showing significant association between saliency cost and the CAPEp scores (β(±SE)=7.26(3.29), $X^2_{(df=1)}$=4.86, p=.027) and at a trend with the AQ scores (β(±SE)=8.34(4.50), $X^2_{(df=1)}$=3.43,

p=.064). The interaction term of the AQ scores x CAPEp scores was negatively associated with saliency cost (β(±SE)= -.39(.17), $X^2_{(df=1)}$=5.35, p=.021).

To probe the nature of the interaction term, we followed the method by Hayes and Matthes whereby the effect of one predictor on saliency cost is examined at the mean, one standard deviation below the mean and one standard deviation above the mean of the other predictor (Hayes and Matthes, 2009). Figure 4.4A visualizes the interaction between psychosis and saliency cost by plots of simple regression lines at low AQ (AQ=9.96), average AQ (AQ=16.25), and high AQ (AQ=22.54), and Figure 4.4B visualizes the interaction between autism tendencies and saliency cost at low CAPEp (CAPEp=22.19), average CAPEp (CAPEp=27.25), and high CAPEp (CAPEp=32.31). To identify the region of the moderator variable where the predictor has a significant effect (i.e., p<.05) on the outcome measure (i.e., saliency cost), we used the Johnson-Neyman method (Hayes and Matthes, 2009). According to this analysis, psychosis proneness (Figure 4.4A) significantly increases saliency cost in individuals scoring below 9 on the AQ scale, and significantly reduces it in individuals scoring above 29 on the AQ. This suggests that individuals with higher psychosis proneness incur greater saliency cost mainly when they have low AQ scores, and that this effect is attenuated in individuals with high AQ scores. Conversely, saliency cost decreases significantly as a function of autism tendencies (Figure 4.4B) in individuals scoring above 26 on the CAPEp scale, suggesting that autism tendencies are associated with a decrease in saliency cost in individuals scoring about average and above on the CAPEp.

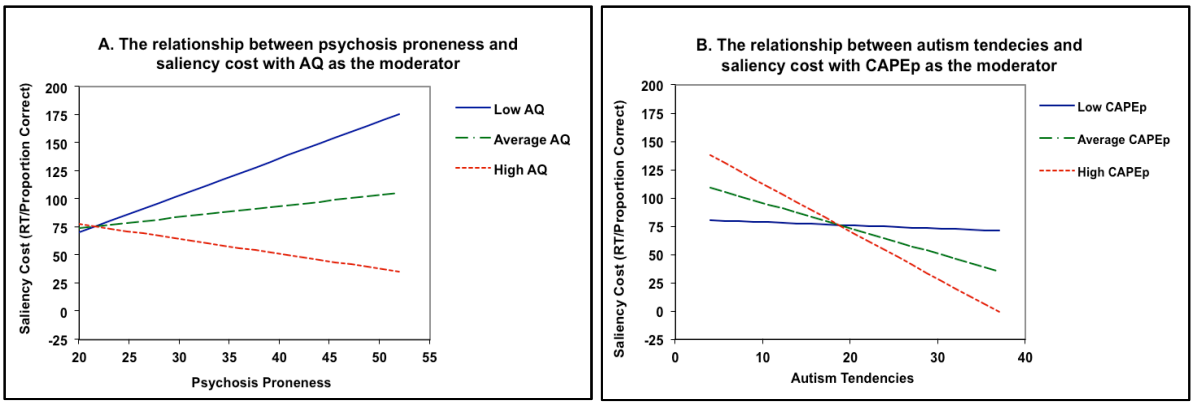

Figure 4.4. (A) Visualizes the association between psychosis proneness and saliency cost by plots of simple regression lines at low (-1 SD), average, and high (+1 SD) AQ scores. (B) Visualizes the association between autism tendencies and saliency cost by plots of simple regression lines at low (-1 SD), average, and high CAPEp scores (+1 SD) as moderators.

Performance as a function of the relative dominance of autism tendencies versus psychosis proneness

The regression analyses using Model 1 indicated that only saliency cost was impacted by autism and psychosis tendencies. Therefore, only saliency cost was used as a dependent variable in Model 2. The overall model was significant ($\chi^2_{(df=5)}$ =11.10, p=.049), with only the bias effect (β(±SE) = -10.11(5.04), Wald$\chi^2_{(df=1)}$ = 4.03, p=.045) and the quadratic term of the mean effect (β(±SE) = -2.97(1.46), Waldχ^2 = 4.18$_{(df=1)}$, p=.041) being significant (see Table 4.1 for summary of regression coefficients). As can be seen from Figure 4.5, the bias effect suggests that saliency cost increases as the bias shifts from autism-dominant to psychosis-dominant individuals. Interestingly, saliency cost is also associated with autism tendencies and psychosis proneness following an inverted U-shaped pattern, along which both autism and psychosis appear to have an additive effect on saliency cost. This, however, seems to be confined to individuals scoring within +/- 2SD from the mean (+2SD > z > -2SD) and is absent in individuals who have low or high balanced expressions on both traits (+2SD < z < -2SD; blue shaded areas in Figure 4.5).

Table 4.1. Summary of regression coefficients of the bias model with saliency cost as the dependent variable, controlling for level difference and congruency interference

Model / Coefficient	β	(SE)	Waldχ^2	df	Sig.
Constant	80.85	6.73	144.24	1	**<.001**
Bias [(AQ-CAPEp)/2]	-10.11	5.04	4.03	1	**=.045**
Bias^2	3.38	2.57	1.73	1	=.19
Mean Effect [(AQ+CAPEp)/2]	-4.74	3.65	1.69	1	=.19
(Mean Effect)^2	-2.97	1.46	4.18	1	**=.041**
Bias x Mean Effect	0.58	2.47	.054	1	=.82

AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences

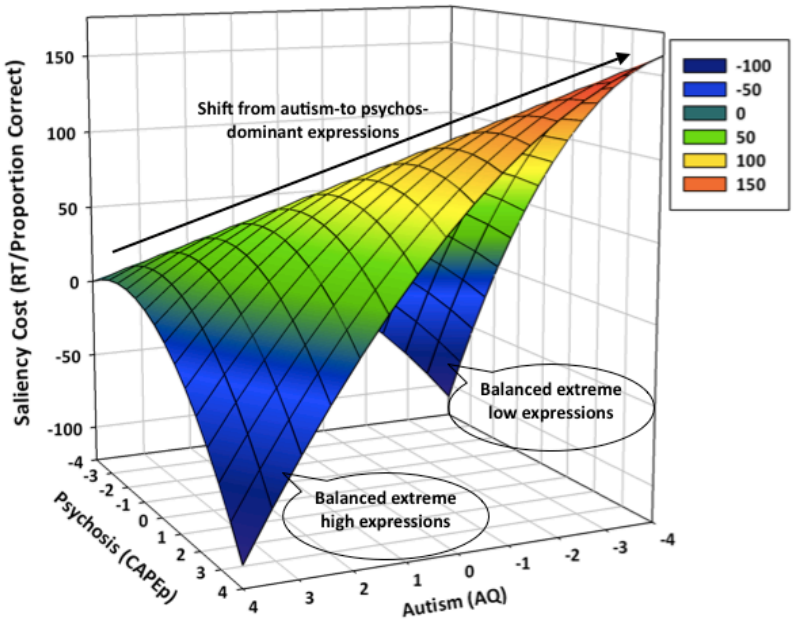

Figure 4.5. Model 2 prediction of saliency cost as a function of autism tendencies and psychosis proneness in the Global-Local Task. Values on the autism and psychosis axes represent Z standardized scores on the AQ and the positive subscale of the CAPE. Negative/Positive values indicate scores below/above the mean. The arrow line at the ridge of the surface is depicted to aid visualization of the effect of the shift from autism-dominant to psychosis-dominant expressions on saliency cost. Bubbles highlight the zone of extreme low and high balanced expressions and their similar attenuating effects on saliency cost.

The Face-Scene Perception Task

Five participants were removed from the analysis for failing to follow task instructions, i.e., responding to faces rather than to scenes or vice versa. Thus, data used in the analyses for this task were of 197 participants (42 males, 155 females; mean age = 21.45, SD = 4.35). On average, participants scored 27.25(±4.98) on the CAPEp, 16.25(±6.29) on the AQ, and 12.47(±11.13) on the CESD-R. Significant Spearman's ρ correlations were observed between the AQ and CAPEp scores (r=.32, p<.001), the AQ and CESD-R (r=.38, p<.001) as well as between the CESD-R and CAPEp scores (r=.38, p<.001). There were no associations between gender or age with either the AQ or the CAPEp scores (-.06<*rs*<.08, all *ps*>.26). Age was negatively correlated with the CESD-R scores (r=-.15, p=.036). There were no differences between male and female participants on any of these measures except for age where female (M±SD= 20.94±4.08)) were younger than the male participants (M±SD= 23.31±4.85) (t=2.90; p=.005).

Figure 4.6 shows the results of the participants' performance on the task. The 2x2x3 repeated measure ANOVA reveals a main effect for target ($F(1,196)=58.48$, $p<.001$, $\eta_p^2=.23$) where participants were slower responding to faces (M(SE)= 768.09(18.18) than to scenes (M(SE)=627.97(10.14); a main effect for saliency ($F(1,196)=44.17$, $p<.001$, $\eta_p^2=.18$) where participant were slower overall in the scene salient condition (M(SE)=742.71(15.58) than the face salient condition (M(SE)=653.35(10.63); and a main effect of congruency ($F(2,392)=48.86$, $p<.001$, $\eta_p^2=.20$) where participants were slower in the incongruent (M(SE)=772.47(17.78) than either the congruent (M(SE)=658.23(12.88) or neutral (M(SE)=663.37(9.29) conditions. There was no difference between the congruent and neutral conditions (p=.56). Moreover, the 2-way interactions of target x saliency ($F(1,196)=293.38$, $p<.001$, $\eta_p^2=.60$), target x congruency ($F(2,392)=44.24$, $p<.001$, $\eta_p^2=.18$) and saliency x congruency ($F(2,392)=37.48$, $p<.001$, $\eta_p^2=.16$) were significant, as well as the 3-way

interaction of target x saliency x congruency ($F(2,392)=40.64$, $p<.001$, $\eta_p^2=.17$). Follow-up analysis revealed only a main effect for saliency in the scene condition, where the shift from the scene salient (M(SE)=555.13±7.51) to the face salient condition (M(SE)=700.81±15.86) was associated with increased cost ($F(1,196)=103.51$, $p<.001$, $\eta_p^2=.35$). In the face condition, the analysis revealed a saliency x congruency interaction ($F(2,392)=47.88$, $p<.001$, $\eta_p^2=.20$). In this condition, the shift from face salient to scene salient was associated wit increased cost was significant for the neutral, congruent and incongruent conditions (all *ts*>8.14, all *ps*<.001, Cohen's *d*=.65-1.0). However, as can be seen from Figure 4.6, processing cost was significantly more pronounced in the incongruent condition when compared to the neutral ($t=7.53$, $df=196$, $p<.001$, Cohen's *d*=.71) or congruent conditions ($t=6.95$, $df=196$, $p<.001$, Cohen's *d*=.64). There was no difference between the congruent and neutral conditions ($p=.63$). Collectively, these findings show that the presence of a salient distractor has a measurable cost on target identification.

Figure 4.6. Overall performance on the Face-Scene Perception Task as a function of Target (Face vs. Scene), saliency (Face salient vs. Scene Salient) and congruency (Congruent vs. Incongruent vs. Neutral). Bars represent standard errors.

Estimating the effect of autism tendencies and psychosis proneness on target difference, congruency interference and saliency cost

First, Spearman's ρ revealed no correlations between age or depressive mood on any of the dependent variables (i.e., target difference, congruency interference and saliency cost). There were however significant associations between target difference and congruency interference (r=.24, p=.001), target difference and saliency cost (r=.50, p<.001), as well as congruency interference and saliency cost (r=.40 , p<.001). There were also no differences between male or female participants on any of these measures. Accordingly, each dependent measure was entered into a regression model with the AQ scores, CAPEp scores and their interaction (AQxCAPEp) as predictors, after controlling for the other two measures in separate regression models to remove any shared variation. Thus, the dependent measures in these models are the residuals from the original regression models. The overall models for the target difference ($\chi^2_{(df=3)}$ =4.42, p=.22) and the congruency interference ($\chi^2_{(df=3)}$ =3.71, p=.30) were nonsignificant, suggesting that neither target selection nor the presence or absence of response conflict is affected by inter-individual differences on autism or psychosis. In contrast, the regression model estimating saliency cost was significant ($\chi^2_{(df=3)}$ =18.94, p<.001), with parameter estimates showing significant association between saliency cost and CAPEp scores (β(se)=23.47(9.97), $X^2_{(df=1)}$=10.56, p=.001) and at a trend with the AQ scores (β(se)=17.90(7.22), $X^2_{(df=1)}$=3.22, p=.073). The interaction term of AQ scores x CAPEp scores was also significant but negatively associated with saliency cost (β(se)=-.79(.37), $X^2_{(df=1)}$=4.52, p=.034).

We probed the interaction following the same analysis we applied in the Local-Global task. Figure 4.7A visualizes the interaction between psychosis and saliency cost by plots of simple regression lines at low AQ (AQ=9.95), average AQ (AQ=16.25), and high AQ (AQ=22.54), and Figure 4.7B visualizes the interaction between autism tendencies and

saliency cost at low CAPEp (CAPEp=22.27), average CAPEp (CAPEp=27.25), and high CAPEp (CAPEp=32.23). According to the Johnson-Neyman method, psychosis proneness has a significant effect on saliency cost (i.e., $p<.05$) in individuals scoring below 23 on the AQ (Figure 4.7A), suggesting that the effect of psychosis on saliency cost was not detectable in individuals with high scores on the AQ scale. Conversely, saliency cost decreases significantly as a function of autism tendencies in individuals scoring above 27 on the CAPEp scale (Figure 4.7B), suggesting that autism tendencies are associated with a decrease in saliency cost in individuals scoring above average on the CAPEp.

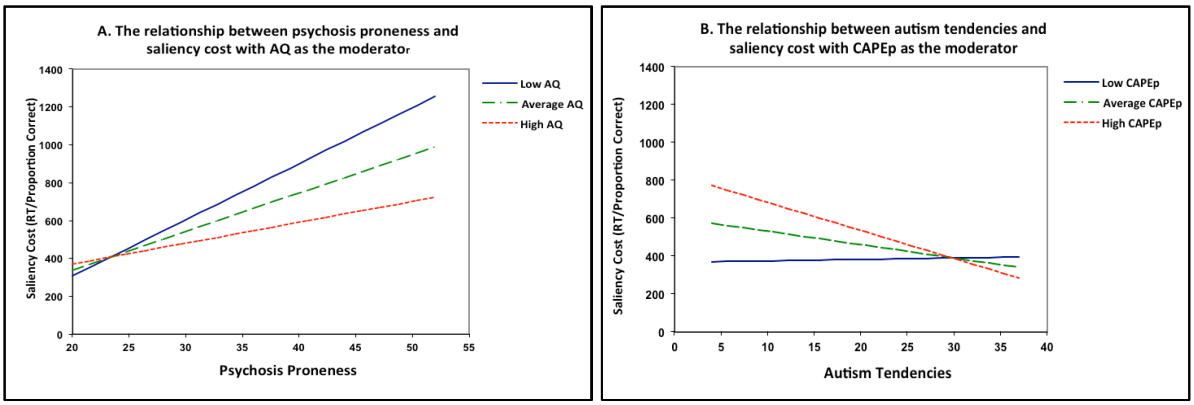

Figure 4.7. (A) Visualizes the association between psychosis proneness and saliency cost by plots of simple regression lines with low (-1 SD), average, and high (+1 SD) AQ scores. (B) Visualizes the association between autism tendencies and saliency cost by plots of simple regression lines with low (-1 SD), average, and high CAPEp scores (+1 SD) as moderators.

Estimating the effect of autism tendencies and psychosis proneness on performance during the neutral condition

We investigated the association of autism, psychosis and their interaction on the cost incurred during the neutral condition only to see if they also explain simple effects of perception. The omnibus test of the overall model was not significant ($\chi^2_{(df=3)}$ =7.09, p=.07) or any of its parameter estimates (all *ps*>.18).

Performance as a function of the relative dominance of autism tendencies versus psychosis proneness

The results of the regression analyses using Model 1 indicated that only saliency cost was impacted by autism and psychosis tendencies. Therefore, only saliency cost was used as a dependent variable in Model 2, controlling for target difference and congruency interference. Using generalized linear models, the model was significant ($\chi^2_{(df=7)}$ =97.65, p<.001), with only the bias (β(±SE) = -33.30(10.96), Wald$\chi^2_{(df=1)}$ = 9.24, p=.002) and the quadratic term of the bias (β(±SE) = 14.77(5.51), Wald$\chi^2_{(df=1)}$ = 7.18, p=.007) being significant (see Table 4.2 for summary of regression coefficients). As can be seen from Figure 4.8, saliency cost is associated with the relative dominance of autism tendencies or psychosis proneness, following a U-shaped pattern, along which saliency cost increases as it shift from autism dominant individuals to psychosis dominant individuals. While U-shaped pattern of this figure contrasts with Figure 4.5 of the Global-Local task, they are similar in that, in both, saliency cost increases as the bias shifts from autism-dominant to psychosis-dominant individuals. Interestingly, individuals presenting with similar level of expression in autism and psychosis including individuals with low scores or high scores on both scales, are similarly impacted by the cost incurred by salient distractors (Figure 4.8). However, unlike the Global-Local task where the effect is confined to individuals at the extreme distribution of biased scores, the effect on saliency cost, in the Face-Scene task, is driven by the entire range of the bias scores.

Table 4.2. Summary of regression coefficients of the bias model with saliency cost as the dependent variable, controlling for target difference and congruency interference

Model / Coefficient	β	(SE)	Waldχ^2	df	Sig.
Constant	156.88	16.41	91.46	1	**<.001**
Bias [(AQ-CAPEp)/2]	-33.30	10.96	9.24	1	**=.002**
Bias^2	14.77	5.51	7.18	1	**=.007**
Mean Effect [(AQ+CAPEp)/2]	7.37	7.82	0.89	1	=.35
(Mean Effect)^2	-4.99	3.10	2.59	1	=.11
Bias x Mean Effect	-4.93	5.28	0.87	1	=.35

AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences

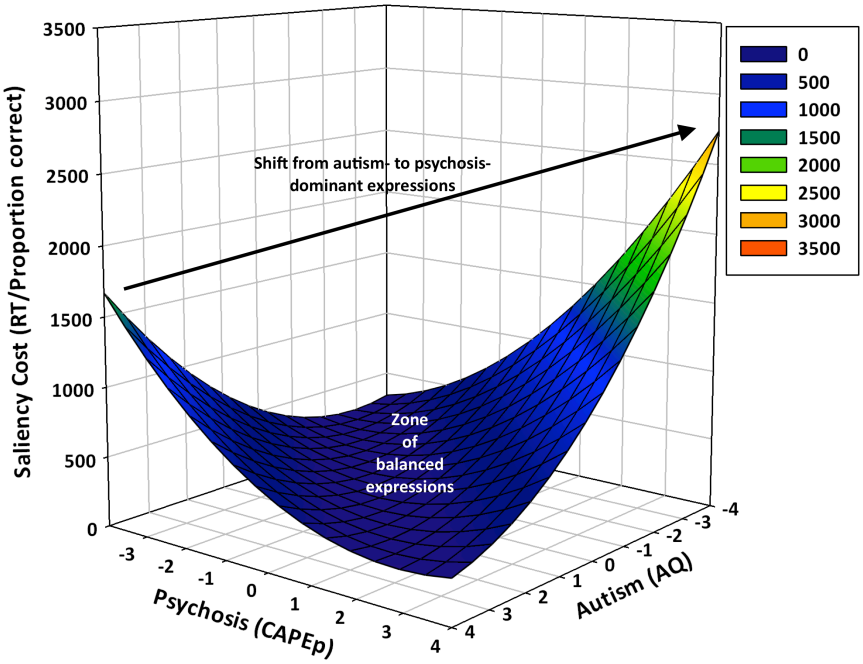

Figure 4.8. Model 2 prediction of saliency cost as a function of autism tendencies and psychosis proneness in the face-scene perception task. Values on the autism and psychosis axes represent Z standardized scores on the AQ and positive subscale of the CAPE. Negative/Positive values indicate scores below/above the mean. The arrow line across the 3-D space is depicted to aid visualization of the effect of the shift from autism-dominant to psychosis-dominant expressions on saliency cost. White text highlights the zone of balanced expressions of autism and psychosis where the effect on saliency cost is the lowest.

DISCUSSION

Our study provides converging evidence suggesting that autism tendencies and psychosis proneness have an interactive effect on saliency cost, such that the effect of the expression of one condition depends on the expression level of the other condition (Figures 4.4 and 4.7). This effect was unrelated to the tasks variables (i.e., level/target or congruency), suggesting that this interactive effect is specific to salience suppression, or, in other words, to attentional rather than perceptual abilities. These findings suggest that previous reports assessing saliency as a function of one trait without assessing the other need to be viewed with some caution. We argue that unmeasured differences in the proportion of one trait in a sample that was intended to look at the other trait might adversely affect results, and might account for some inconsistencies in previous literature. This renders previous literature reporting main effects associating ASD or SSD with saliency cost difficult to interpret with confidence, particularly for studies with small samples, where the chances of getting an unrepresentative range of variance due to ASD or SSD would be higher.

This interactive modulation of autism and psychosis on saliency cost is further clarified in our analyses of the data in terms of mean and bias effects. They show that saliency cost is largely driven by the relative expression of these traits (i.e., the bias effect), with salient distractor stimuli conferring most cost in psychosis-dominant individuals (as compared to autism-dominant individuals), and least in individuals presenting with either balanced low or balanced high expressions of both autism and psychosis tendencies (Figures 4.5 and 4.8). While this striking trend is observed in both experiments, a key difference is that the low saliency costs in the Global-Local task are only observed at the extremes (i.e., in individuals scoring ±2D from the mean on the AQ and the positive subscale of the CAPE), whereas the low saliency costs in the Face-Scene task are observed across the full range of a "balanced" set of autism and psychosis traits. It is tempting to attribute this difference to the

inherent differences across the two tasks (e.g., the way saliency was manipulated, the use of a single objects with two dimensions in the Global-Local task vs. two separate superimposed objects for the Face-Scene task). However, this does not provide a straightforward explanation, and so future work will be necessary to determine whether such differences are robust over a wider range of tasks that manipulate the salience of attended versus ignored aspects of the stimuli.

Overall, our findings are commensurate with the diametric model of autism and schizophrenia spectrum disorders (Crespi & Badcock, 2008) positing that autism and schizophrenia exert opposing effects on cognition and behavior, and suggests that saliency cost is diametrically modulated by phenotypic traits that are disorder-specific. If so, what mechanism might account for this attenuating effect? Examining attentional processes in ASD and SSD may hold clues to the mechanism by which this attenuating effect is achieved. Studies suggest individuals with ASD show increased focus of attention (Baron-Cohen et al., 2001; Blaser et al., 2014; Russell-Smith et al., 2010), whereas individuals with positive SSD (i.e., those who predominantly show positive symptoms) show overswitching (Yogev, Hadar, Gutman, & Sirota, 2003; Yogev et al., 2004). Within the context of our tasks, participants are required to attend to task-relevant information and to filter out salient but task-irrelevant distracting information. This can be achieved by increasing attentional focus or by resisting the tendency to switch or reorient attention. Maintaining attentional focus and reorienting attention are respectively associated with the coordinated action of the top-down dorsal and bottom-up ventral frontoparietal networks (Corbetta, Patel, & Shulman, 2008). This surprising pattern could be accounted for by supposing that autism tendencies and psychosis proneness may be associated with contrasting effects on these networks. Specifically, we suggest that the attenuated effect of salient distractor stimuli as a function of increased expression of autism tendencies is associated with strong top-down modulation. Conversely,

we predict that the effect of the salient distractor as a function of increased expression of psychosis proneness is associated with a strong bottom-up modulation. This corresponds with the notions of proactive and reactive cognitive control (Braver, 2012). In proactive control, individuals bias attention by maintaining goal-relevant information and preventing interference in an anticipatory manner before the onset of the stimulus. In reactive control, individuals respond "online" to interference after the onset of the stimulus. In dealing with distractors, there is evidence suggesting that individuals with schizophrenia differentially rely on reactive control (Lesh et al., 2013), whereas individuals with high autism traits appear to show enhanced proactive control (Mevorach, Spaniol, & Shalev, 2015). As deficits in proactive control processes in schizophrenia have been associated with reduced lateral prefrontal-parietal recruitment (Lesh et al., 2013), we predict increased prefrontal-parietal recruitment in autism.

Our study is the first to observe that co-occurring autistic and psychotic traits can exert opposing influences on saliency cost, and raises the intriguing possibility that saliency-related abnormalities may be attenuated in individuals with comorbid autism and schizophrenia. The similar performance of individuals presenting with low or high expressions of both disorders suggests that the effect of distractor stimuli on information processing is possibly modulated by contrasting attentional mechanisms—increased focused of attention (characteristic of autism) and increased attention switching (characteristic of psychosis). Our findings thus imply that phenotypic variation in individuals diagnosed with either condition are likely to be a reflection of the relative expression of one disorder vis-à-vis the other. As intervention in both ASD and SSD are likely to be different, assessing the relative expression of both autism and psychosis is important for tailoring individualized therapeutic approaches, and particularly for those who meet diagnostic criteria of both disorders. In this context, our analytical approach of indexing these disorders (or expression

thereof) in terms of bias and mean effects is potentially a useful framework to understanding the effect co-morbid conditions have on outcome and behavior.

CHAPTER 5

RE-IMAGING THE INTENTIONAL STANCE IN A COMPETITIVE GAME[7]

[7] This chapter is currently in preparation for submission: Abu-Akel, A., Apperly, I.A., Wood, S.J., Hansen, P.C. (in prep.). Re-imaging the intentional stance in a competitive game. Manuscript in preparation.

ABSTRACT

The commonly-used paradigm to investigate Dennet's "intentional stance" compares neural activation when participants compete with a human versus a computer. This paradigm confounds orthogonal factors: whether the opponent is natural or artificial; and whether the opponent is intentional or an automaton. Findings in existing literature could be due either to variation in participants' use of the intentional stance for mentalizing, or to variation in their response to interacting with a human versus a computer, or to some combination of these. This fMRI study is the first to investigate the intentional stance by orthogonally varying perceptions of the opponents' intentionality (they responded actively and freely or passively according to a script) and their embodiment (they were a human or a computer). The mere perception of the opponent (whether human or computer) as intentional activated the mentalizing network: the temporo-parietal junction (TPJ) bilaterally, right temporal pole, anterior paracingulate cortex and the precuneus. Interacting with humans versus computers induced activations in a more circumscribed right lateralized sub-network within the mentalizing network, consisting of the TPJ and the anterior paracingulate cortex, possibly reflective of the tendency to spontaneously attribute intentionality to humans. The interaction between intentionality (Active versus Passive) and opponent (Human versus Computer) recruited the left frontal pole, possibly in response to violations of the default intentional stance towards humans and computers. These findings expand on earlier research investigating human-computer interactions in various social games, and emphasize the importance of employing an orthogonal design to adequately capture Dennett's conception of the intentional stance as a mentalizing strategy that can apply equally well to humans and other intentional agents.

INTRODUCTION

To what extent do the cognitive and neural processes involved in playing a competitive game

depend on whether one's interactive partner is human? This question not only bears upon theories about the nature of social cognition (Gallagher & Frith, 2003). It is also of relevance to our everyday lives, in which we interact increasingly with artificially intelligent agents such as robots, computers and avatars, and in which our live interactions with other humans are increasingly mediated through electronic media. A burgeoning literature on social neuroscience has associated such interactions with two types of processes. One is theory of mind or mentalizing, which is typically viewed as "cold cognition" about the beliefs, desires and intentions of one's interactive partner (Harvey & Penn, 2010). Mentalizing focuses on the partner's status as a rational, intentional agent, with little regard for the nature of their affective and physical embodiment, and has consistently been associated with activations in the posterior superior temporal sulcus (pSTS)/temporo-parietal region (TPJ) and the medial prefrontal cortex (MPFC) (including the anterior paracingulate cortex (aPCC)). A second type of process is mirroring, which is typically viewed as "flesh-and-blood" simulation of a partner's physical actions and affective reactions (Becchio et al., 2012; Berthoz, Armony, Blair, & Dolan, 2002; Decety, Jackson, Sommerville, Chaminade, & Meltzoff, 2004; Schulte-Ruther, Markowitsch, Fink, & Piefke, 2007). In contrast to mentalizing, mirroring focuses on the partner's embodiment, with little regard for the explicit content of their thoughts. While mirroring is commonly associated with activation in the parietal lobule, the premotor cortex and the inferior frontal gyrus, there is also evidence for mirroring properties in brain regions associated with mentalizing, including the TPJ and the anterior medial prefrontal cortex (Becchio et al., 2012; Hogeveen et al., 2015). In the present study we investigated the processes involved in playing a competitive game by orthogonally varying perceptions of the interactive partner's intentionality (they responded freely or according to a script) and their embodiment (they were a human or a computer).

In a very influential paper, titled "Imaging the Intentional Stance", Gallagher and

colleagues were the first to employ the human-player versus computer-player contrast in a neuroimaging study (Gallagher et al., 2002). In this study, volunteers were asked to play a version of the 'rock, paper, scissors' game against a human opponent or a computer following simple rule-based strategy. In comparing the two conditions (Human $_{\text{minus}}$ Computer), only the anterior paracingulate cortex (PCC; BA 9/32, bilaterally) was differentially active. Several studies employing various interactive games followed, using a similar script according to which participants were led to believe that they were playing either against a human opponent or a computer (Chaminade et al., 2012; Kircher et al., 2009; Krach et al., 2008; Rilling, Sanfey, Aronson, Nystrom, & Cohen, 2004; Takahashi et al., 2014). For example, Kircher et al. (2009) reported stronger activations in the MPFC and the thalamus when playing the Prisoner's Dilemma Game against a human than against a computer. In a later study, using a variant of the 'rock, paper, scissors' game, Chaminade et al., (2012) reported bilateral activation in the MPFC and TPJ and the right thalamus when contrasting participants playing against a human versus playing a computer generating moves at random. In a further contrast between the human and a robot that participants believed to be endowed with artificial intelligence, only the TPJ was active, leading the authors to conclude that the TPJ was specifically involved in mentalizing about humans. Importantly, in this recent study the human player was presented at all times as an "intentional agent" with a calculated strategy to win.

However, while these studies drew inspiration from a prominent theoretical account of mentalizing – Dennet's "intentional stance" theory (Dennett, 1987) – they do not accurately capture Dennet's original conception. Dennett (1987) summarizes the intentional stance as follows "Here is how it works: first you decide to treat the object whose behavior is to be predicted as a rational agent; then you figure out what beliefs that agent ought to have, given its place in the world and its purpose. Then you figure out what desires it ought to

have, on the same considerations, and finally you predict that this rational agent will act to further its goals in the light of its beliefs. A little practical reasoning from the chosen set of beliefs and desires will in most instances yield a decision about what the agent ought to do; that is what you predict the agent will do." (p.17). Dennett takes great care to point out that the stance may be adopted towards any object (animal, vegetable or mineral), but that its utility naturally depends upon the degree to which that object fulfills the stance's assumption that it is a rational agent. In other words, the intentional stance applies just as appropriately to all rational agents, including humans and artificially intelligent robots and computers, and it applies just as inappropriately to humans who lack rationality or free will as it does to pocket calculators. This means that the commonly-used paradigm of comparing neural activation when participants compete with a rational human agent and a computer that follows simple rules actually confounds orthogonal factors: whether the opponent is natural or artificial; and whether the opponent is a rational, intentional agent or an automaton. Existing results in the literature could be due either to variation in participants' use of the intentional stance for mentalizing, or to variation in their response to interacting with a human versus a computer (via mirroring, or some other process), or to some combination of these. The present study is the first in the literature to de-confound these factors in a fully orthogonal design.

Orthogonal variation of the type of competitor and their level of intentionality yields four conditions, the participant plays against one of: an actively competitive human; a non-competitive human who passively follows a predetermined response script; an actively competitive computer endowed with artificial intelligence; and a non-competitive computer that passively follows a predetermined response script. Main effects of the level of intentionality (Active vs. Passive responses) should identify those brain regions involved in deploying the intentional stance in the manner envisaged by Dennett – that is to say, irrespective of whether the target is human or computer. To the degree that mentalizing is

well-characterized as the adoption of an intentional stance, this main effect should overlap with brain regions commonly associated with mentalizing. Main effects of the type of competitor (Human vs. Computer) should identify brain regions that are distinctively involved in interacting with humans rather than computers, and as described above, the existing literature leads to the prediction that this might involve circumscribed regions within the mentalizing network, namely the TPJ and the MPFC, and perhaps a broader set of regions associated with mirroring. Finally, our design offers participants the opportunity to interact with an *intentional* active computer and a *non-intentional* passive human, which are orthogonal to stances we normatively attribute to these agents. Thus, the interaction between the Intentionality and Competitor Identity factors should identify those brain regions in which the demands of deploying the intentional stance depend on the nature of the competitor. Although the expectation that humans are a special target for mentalizing is a mischaracterization of Dennett's intentional stance theory, there are of course other reasons why this expectation is plausible. Most obviously, humans are surely the most frequent target for mentalizing outside of experimental contexts. This might lead the intentional stance to be the default stance towards humans but not computers, one possible outcome of which is disproportionately large effects for the human intentional opponent.

METHODS AND MATERIALS

Participants

24 right-handed, English-proficient healthy adults (5 males; 19 females; mean age (SD) = 21.21±4.21)) participated in the study. Exclusion criteria included having a history of psychiatric illness, epilepsy, neurological disorders, brain injury as well as current alcohol or substance abuse problems. In addition, standard MRI exclusion criteria were considered in this study. These included claustrophobia, recent surgery or trauma, the presence of

ferromagnetic material in the body, including ferromagnetic implants or pacemakers, excessive obesity, excessive tattoos, as well as the inability to lie still for more than and hour. None of the participants were excluded for any of the above criteria.

Materials and procedures

In the pre-screening session, English reading proficiency was assessed with the Test of Irregular Word Reading Efficiency (TIWRE) (Reynolds & Kamphaus, 2007) and the Test of Word Reading Efficiency (TOWRE) (Torgesen, Wagner, & Rashotte, 1999) questionnaires. Handedness was ascertained with the modified Annett Handedness Questionnaire (Annett, 1972). During the scanning session, participants performed two tasks. The first was a computerized version of the Rock, Paper, Scissors game. The second was Hartwright et al.'s (Hartwright et al., 2012) British English variant of Saxe and Kanwisher's theory of mind (ToM) functional localizer task (Saxe & Kanwisher, 2003). At the end of the scanning session, all participants went through a debriefing interview. The study was approved by the University of Birmingham Research Ethics Committee, and written informed consent was obtained from all participants.

The rock, paper, scissors (RPS) task[8]

In this task, participants were required to predict the moves of their opponent in order to win. The game has the following simple rules: Rock beats scissors, paper beats rock, and scissors beat paper. The winner of each round was awarded 1 point. A no-response resulted in an automatic win for the opponent, and identical moves resulted in a draw and no points were awarded. Here we orthogonally manipulated the intentional stance during the game in such a way that the participants were led to believe that they were playing under four conditions: (1)

[8] We thank Hannah Widdman for helping prototype an initial version of the RPS task.

against an *active* human agent who was a professional RPS player, (2) a *passive* human agent who followed a predetermined response script, (3) an *active* intelligent computer program (called AIRPS) that was capable of analyzing the participant's strategy, and (4) a *passive* computer program that followed a predetermined response script.

Participants were cautioned not to use a stereotyped strategy and to play competitively with the intention of beating their opponent. Feedback was provided during the scan sessions as to how well the participant was scoring at the end of each block of ten rounds of the game and a summary of the results at the end of each fMRI run. Positive scoring and effort were rewarded with a prize of £10 for the highest performing participant overall at the end of the study. Before each one of the four conditions, participants were provided with on-screen instructions to remind them of what they were required to do and which opponent they would be playing. These instructions were also used to induce a shift in the participant's stance towards their opponent. To reinforce the impression that the participant was truly playing against a '*human*' opponent, a 3% fallibility 'no-response' measure was embedded during the human conditions. It is important to note that he "intentional stance" is one among three different stances – the others being design stance and physical stance. There may be degrees of intentional stance, but we're not deliberately investigating these here.

Crucially, unbeknownst to the participants, the game was always played against a computer program generating moves entirely at random. The design ensured that the only difference across the conditions was the particular stance the participant was adopting under the various conditions. Of course, there was always the possibility that participants would not behave in the expected manner under the various conditions. Accordingly, a briefing procedure was utilized after the scanning session during which participants were asked to recount how they understood and experienced these conditions. This information was

gathered to ascertain the intentional stance adopted and the different strategies that the participants may have used under the various conditions. None of the participants expressed doubt regarding the identity of the four opponents and all reported experiences of intentional interactions with the opponents such that it was more difficult to play the professional human (indicated by 21 participants) and harder to predict AIRPS (indicated by 16 participants). Participants also indicated that they were more anxious to play the professional player (16 participants).

The RPS experiment consisted of 5 fMRI runs, each lasting 440s per run (~40mins total). Each fMRI run consisted of 4 blocks, representing the four conditions of interest. The sequence of opponents was chosen from 8 predetermined player-sequences (chosen from the 24 possible sequences) such that on each sequence the human and the computer opponents were presented in alternating order. On four of the sequences, the participants' first opponent was a human and on the remaining four a computer (see Table 5.1). The sequences the participants' played, in each of the 5 fMRI runs, were selected in a pseudorandom order in the following manner: The 1st participant played sequences 1 through 5, the 2nd participants played sequences 6,7,8,1,2, the 3rd participant played sequences 3,4,5,6,7,8, and so forth.

Table 5.1. Presentation of the 8 player sequences used in the RPS task

Player Sequence_1	H1	C1	H2	C2
Player Sequence_2	H1	C2	H2	C1
Player Sequence_3	H2	C1	H1	C2
Player Sequence_4	H2	C2	H1	C1
Player Sequence_5	C1	H1	C2	H2
Player Sequence_6	C1	H2	C2	H1
Player Sequence_7	C2	H1	C1	H2
Player Sequence_8	C2	H2	C1	H1

H1= Active human; H2=Passive Human; C1= Active Computer; C2=Passive Computer.

Each block was preceded by a 10s period during which the instructions were displayed, and followed by a 30s rest period. During each block the participant played 10 trials against one of the four possible opponents. Response selections (i.e., rock, paper or scissors) were made using a button box with three active buttons that was placed in the participant's left hand. Figure 5.1 presents a schematic representation of stimuli presentation and timing during each trial. All participants went through a practice session of 2 blocks outside the scanner. The experiment was presented using Presentation (Neurobehavioral Systems, CA), which also recorded the behavioral data (button pressed and reaction time).

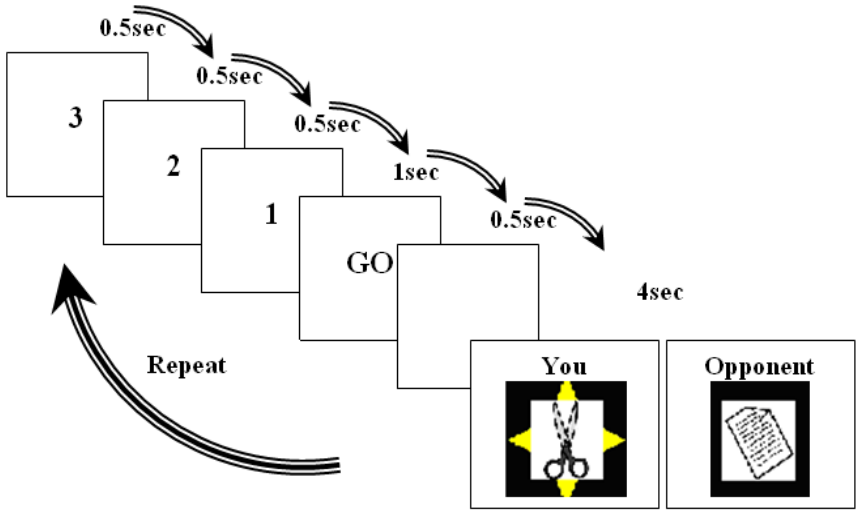

Figure 5.1. Each trial began with a countdown 3, 2, 1, in 0.5s intervals, followed by 'GO' during which the participants made their moves. The 'GO' was present for 1s followed by a 0.5s blank screen. The results screen is then displayed for 4s indicating the moves drawn by both players and the outcome. Winning move is displayed with a yellow star.

The theory of mind (ToM) localizer task

This task was used to reliably identify regions within the mentalizing network, which include the TPJ, the paracingulate/medial prefrontal cortex and precuneus and the temporal pole. In this experiment, we used Hartwright et al.'s (Hartwright et al., 2012) anglicized variant of the Saxe and Kanwisher's task (Saxe & Kanwisher, 2003) during which participants read 24 short vignettes that were displayed on the screen for 10 seconds. Half of the stories described the false belief of a character about the current state of affairs (i.e., the False Belief (FB)

stories), and the other half described a physical event that is non-concurrent with reality such as a photo of a past event (i.e., the False Photograph (FP) stories). Each story was followed by a true-false question that was displayed for 4 seconds, and to which they responded using a response box with two active buttons that was placed in the participant's left hand. The task consisted of four short fMRI runs. In each run, six stories, 3 FB and 3 FP, were presented in an alternating order, interleaved with a 12.5sec rest period. All participants went through a practice session of four trials outside the scanner. The experiment was presented using Presentation (Neurobehavioural Systems, CA), which also recorded the behavioral data (response selection and reaction time).

fMRI data acquisition and analysis

Data were acquired in a single scanning session using a 3T Philips Achieva scanner. 176 T2*-weighted standard echo planar imaging (EPI) volumes were obtained in each of the RPS task runs, using a 32 channel head coil. Parameters used to achieve whole brain coverage are as follows: TR=2.5s, TE=35ms, acquisition matrix = 80 x 80, flip angle =83°, isotropic voxels 3x3x3 mm^3, 42 slices axial acquisition obtained consecutively in a bottom-up sequence. Using the same parameters, 71 EPI volumes were acquired for each run of the localizer task. A T1-weighted scan was then acquired as a single volume at higher spatial resolution as a 3D TFE image (matrix size 288x288, 175 slices, sagittally acquired and reconstructed to 1x1x1 mm^3 isotropic voxels. TE =3.8ms. TR = 8.4 ms).

Preprocessing and statistical analyses of the data were performed using the FMRIB software library (FSL version v.5.0.6; FMRIB, Oxford, www.fmrib.ox.ac.uk/fsl). For both experiments, initial preprocessing of the functional data consisted of slice timing correction, and motion correction (MCFLIRT). The blood oxygen level dependent (BOLD) signals were high-pass filtered using a Gaussian weighted filter to remove low-frequency drifts in the bold

signal. Spatial smoothing of the BOLD signal was performed using a 5mm full-width-half-maximum kernel. The functional data were registered to their respective structural images and transformed to a standard template based on the Montreal Neurological Institute (MNI) reference brain, using a 6-DoF linear transformation (FLIRT).

RPS task experiment analysis

Playing against a computer or a human, with either agency or by following a script, provided the four baseline conditions. These four conditions comprised a 2x2 ANOVA experimental design with factor 1 being the human vs. computer opponent and factor 2 being the element of implied agency from the opponent (active vs. passive). Condition regressors were convolved with the canonical hemodynamic response function within a general linear model framework (GLM). A high-pass filter with a cut-off of 105s was used. Motion parameters were treated as regressors of no interest in order to account for unwanted motion effects. Session data were aggregated per participant using a second level fixed effects model. Third level modeling was used to aggregate the data across participants in a 2x2 repeated measures ANOVA with Active vs. Passive and Human vs. Computer as within subjects factors, employing a mixed effects analysis with cluster based thresholding at $Z > 2.3$, $pcorr < 0.05$.

Localizer task experiment analysis

The localizer task was modelled as per Hartwright et al. (2012). The FB and the FP conditions were convolved with a gamma-derived canonical hemodynamic response function within a GLM. A high-pass filter with a cut-off of 21s was used. Second and third level modeling were used to aggregate the data across sessions and participants for the contrast of interest FB > FP. Individual's participant session data was aggregated using a fixed effects model at second level, and the group data were aggregated at third level using a mixed effects analysis with cluster based thresholding at $Z > 3.6$, $pcorr < 0.05$.

Overlap analysis

Overlap analysis between the thresholded data ($Z > 2.3$, $p\text{corr} < 0.05$) for the Human > Computer and the Active > Passive contrasts was conducted to identify shared activations across the two thresholded contrasts. We also conducted an overlap analysis between these two contrasts and the FB > FP contrast of the ToM localizer task. The analysis we conducted with FSL's *easythresh* function (Nichols, Brett, Andersson, Wager, & Poline, 2005).

RESULTS

Whole brain analysis: RPS task

A 2×2 repeated measures ANOVA of the RPS task identified main effects of the game partner (Computer vs. Human) and intentionality (Active vs. Passive), as well as an interaction between the two factors. Playing an active rather than a passive opponent largely recruited a network of regions associated with mentalizing, which included the TPJ bilaterally, right temporal pole, anterior PCC and precuneus. In addition, the middle temporal gyri were activated. The reverse contrast of Passive $_{\text{minus}}$ Active revealed activation only in the superior parietal lobule. Playing a human rather than a computer, activations were observed in the right TPJ and the anterior PCC only. Here, the reverse contrast of Computer $_{\text{minus}}$ Human revealed bilateral activations in the frontal pole. Intriguingly, the interaction between the implied agency (i.e., whether the opponent is active or passive) and the game partner (i.e., whether the opponent is computer or human) elicited activation in the left frontal pole only, specifically in the (Active Computer x Passive Human) $_{\text{minus}}$ (Passive Computer x Active Human) contrast (see Table 5.2, Figure 5.2).

Table 5.2. Cluster Peaks for the Rock, Paper, Scissors Task

Hemisphere and Region	MNI Coordinates			Z
	X	Y	Z	Value
Active > Passive				
L Angular Gyrus, Lateral Occipital Cortex, Temporoparietal Junction	-44	-60	32	4.94
R Angular Gyrus, Temporoparietal Junction, Supramarginal Gyrus	56	-50	30	4.70
Anterior Paracingulate cortex	-10	44	24	5.16
L/R Precuneous	-8	-60	36	3.90
R Temporal Pole	28	14	-26	4.43
L Middle Temporal Gyrus	-56	-26	-14	4.39
R Middle Temporal Gyrus	60	-20	-16	4.62
Passive > Active				
Superior parietal lobule	36	-52	62	3.97
Human > Computer				
R Angular Gyrus, Lateral Occipital Cortex, Temporoparietal Junction	54	-62	16	3.32
Anterior Paracingulate cortex	10	48	30	3.43
Computer > Human				
L Frontal Pole	-24	44	-18	4.65
R Frontal Pole	18	46	-20	3.38
Interaction [(Active Computer + Passive Human) – (Passive Computer + Active Human)]				
L Frontal Pole	-34	46	-16	4.17

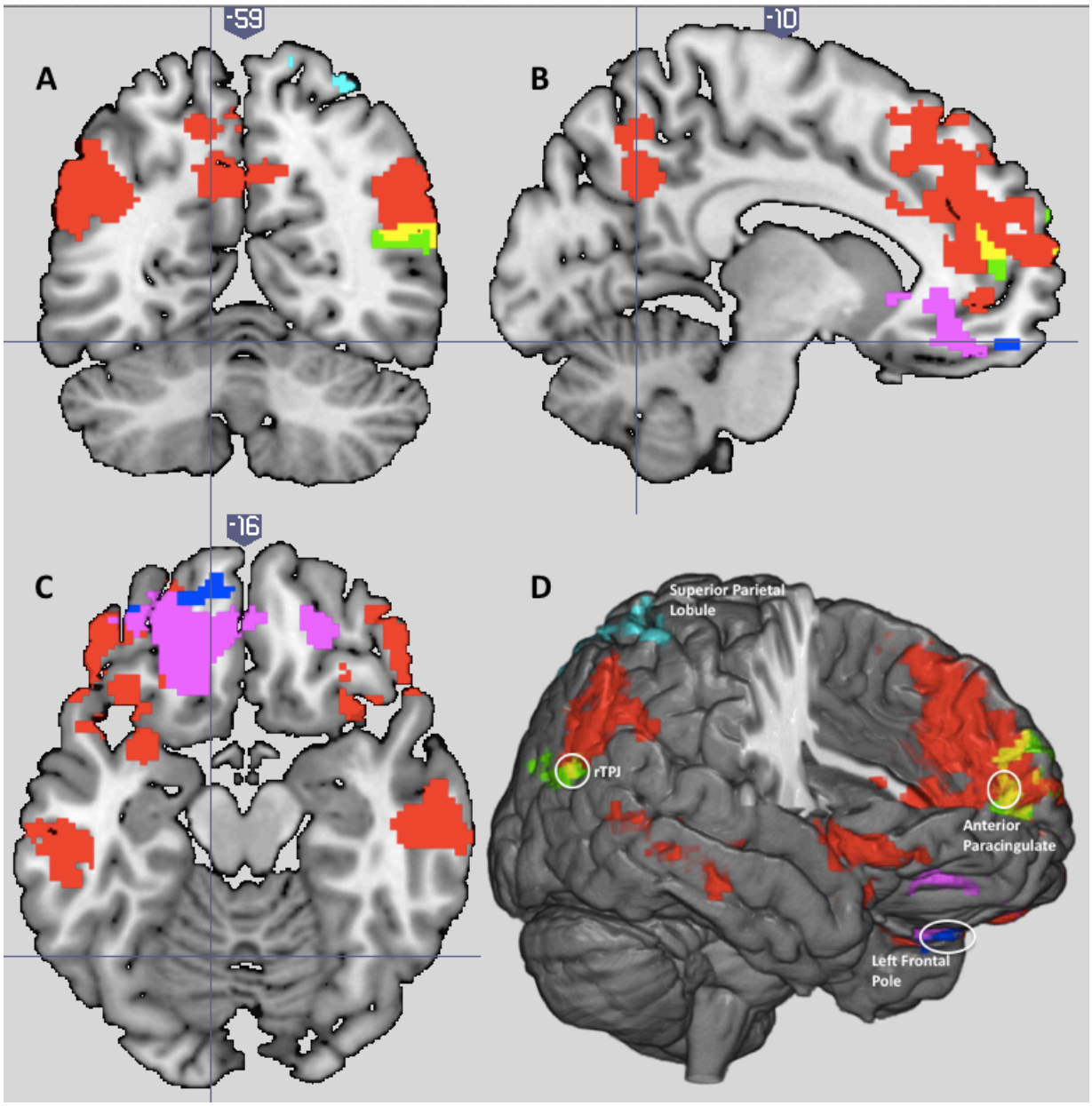

Figure 5.2. Activations of the Active $_{minus}$ Passive contrast (red), Passive $_{minus}$ Active contrast (cyan), Human $_{minus}$ Computer contrast (green), Computer $_{minus}$ Human (Magenta), and the Interaction (blue) are presented in A) on a coronal (Y=-59), B) sagittal (X=-10) and C) axial (Z=-16) planes. Yellow areas in A, B, D reflect overlapping areas between the Active $_{minus}$ Passive and the Human $_{minus}$ Computer contrasts. D is an annotated 3-D summary image. Images are displayed in neurological convention, where left is represented on the left side of the image.

Whole brain analysis: ToM localizer task

The mixed effect analysis of the FB $_{minus}$ FP contrast revealed activations in core regions within the prototypical mentalizing network which included both the left and right TPJ, the

precuneus as well as the medial prefrontal cortex (see Table 5.3). These results are consistent with previous studies using this task (Hartwright et al., 2012; Saxe & Kanwisher, 2003).

Table 5.3. Cluster Peaks for the Theory of Mind Localizer Task

Hemisphere and Region	MNI Coordinates			Z
	X	Y	Z	Value
False Belief > False Photograph				
L Angular Gyrus, Lateral Occipital Cortex, Supramarginal Gyrus, Temporoparietal Junction	-56	-62	28	6.18
R Angular Gyrus, Lateral Occipital Cortex, Temporoparietal Junction	56	-64	30	5.22
L/R Paracingulate cortex, Frontal Pole	0	58	10	5.87
L/R Precuneus	0	-60	30	6.85
L/R Cingulate Cortex	0	-16	34	5.59
R Medial Frontal Gyrus	44	12	50	4.54
R Frontal Orbital	50	30	-16	4.72
L Inferior/Middle Temporal Gyrus	-50	0	-40	5.81
R Inferior/Middle Temporal Gyrus	50	0	-38	6.43
L Cerebellum Crus II	-28	-84	-36	6.25
R Cerebellum Crus II	30	-86	-36	5.09
L Cerbellum IX, Vermis VIIIb	-6	-62	-44	5.04
L Amygdala	-18	-4	-20	4.08

Overlap analysis

The overlap analysis between the Active $_{minus}$ Passive and Human $_{minus}$ Computer revealed shared activation in the paracingulate [-4, 50, 20] and the rTPJ [58, -52, 28]. The Human $_{minus}$ Computer overlapped with the False belief $_{minus}$ False photograph contrast at the right medial frontal gyrus [10, 48, 30], in the vicinity of the paracingulate cortex. Finally, the activations maps in the Active $_{minus}$ Passive and the False belief $_{minus}$ False photograph contrasts overlapped considerably in core regions within the mentalizing network. These included the

TPJ bilaterally [-44, 60, 32; 58, -52, 28], and the paracingulate cortex [-4, 50, 20] (see Figure 5.3).

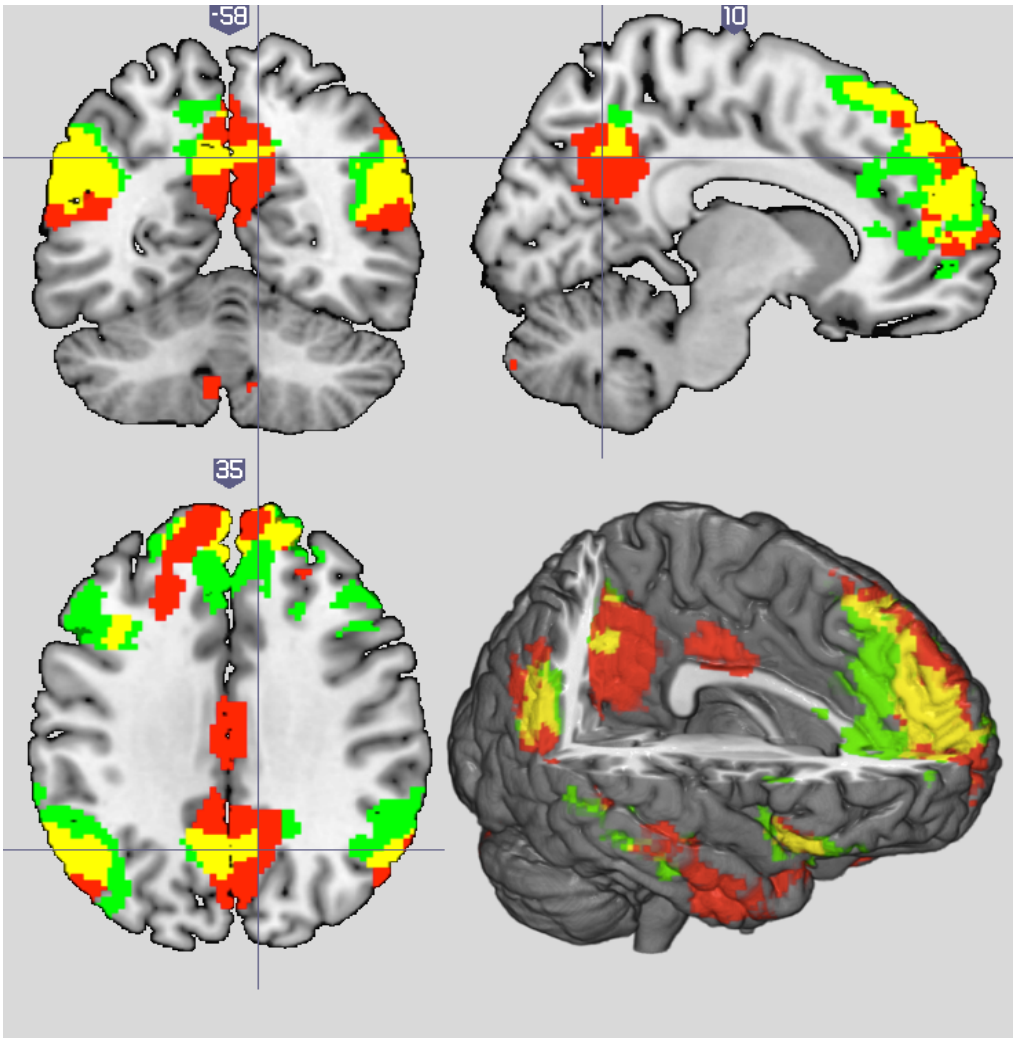

Figure 5.3. Overlaps between the False belief $_{minus}$ False photograph (ToM Localizer Task; Red) and the Active $_{minus}$ Passive contrast (RPS Task, Green), presented on a coronal (Y=-58), sagittal (X=10) and axial (Z=35) planes. Yellow reflects overlapping areas between the Active $_{minus}$ Passive and the False belief $_{minus}$ False photograph contrasts. Only the left TPJ [-44, 60, 32], right TPJ [58, -52, 28] and paracingulate cortex [-4, 50, 20] survived thresholding ($Z > 2.3$, $p$corr < 0.05). Images are displayed in neurological convention, where left is represented on the left side of the image.

DISCUSSION

In the present study, we examined the brain regions recruited when people play an interactive game against an opponent that they took to be either a human or a computer, and either freely intentional or passively following a script. As such, this is the first study in the literature to

de-confound these factors in a fully orthogonal design. A key finding of our study is that a network of regions involved in mentalizing was activated whenever participants believed their opponent to be an intentional agent, irrespective of whether they believed them to be a human or a computer. As presented in Table 5.2 and visualized in Figure 5.2, the main effect of intentionality bilaterally activated the TPJ, the precuneus, the anterior PCC and the right temporal pole. Converging evidence that these are indeed brain regions consistently implicated in mentalizing came from the substantial overlap between these brain regions and those observed during the ToM localizer task (see Figure 5.3). These results are clearly consistent with Dennett's (1987) notion of an intentional stance that applies equally well to human and non-human intentional agents.

The second main contrast, Human $_{\text{minus}}$ Computer, revealed brain activity that was confined to the rTPJ and anterior PCC. One interpretation of these results is that they reflect a process of simulative mirroring of the human opponent that is not applied to the computer opponent because it lacks the participants' embodiment. This interpretation is consistent with the activation of these regions in some previous studies of the mirror network (Cattaneo & Rizzolatti, 2009). However, this interpretation fits less well with the absence of any observation in the present study of activity in premotor cortex or inferior frontal gyrus, which might have been expected if participants were simulating the actions of their human competitors (Molenberghs, Cunnington, & Mattingley, 2012). The absence of these and other "mirroring" effects does not count against an important role for mirroring in social cognition more generally, and may make sense in the current study given that participants were never able to observe their competitor or their actions. This is consistent with the results of a large meta-analysis (of over 200 fMRI studies) showing that the mirror network activated in the presence of observable biological motion and the mentalizing network activated when individuals inferred the intentions of others based on abstract information and in the absence

of any perceivable biological motion (Van Overwalle & Baetens, 2009). As such, this leads us to suggest that the observed activity in rTPJ and anterior PCC for the Human $_{\text{minus}}$ Computer contrast reflects spontaneous mentalizing, rather than mirroring. These two regions have been consistently activated during spontaneous mentalizing in other studies (Ma, Vandekerckhove, Van Overwalle, Seurinck, & Fias, 2011; Mar, Kelley, Heatherton, & Macrae, 2007) and have previously been shown to respond preferentially to action/stimuli that are deemed of human (vs. computer) origin (Stanley, Gowen, & Miall, 2010). Consistent with claims that people have a basic tendency to differentiate humans and computers along the lines of intentionality (Levin, Killingsworth, Saylor, Gordon, & Kawamura, 2013) we suggest that the mere presence of the human competitor in the present study was sufficient to cue participants to think about their mental states, even though the passive human competitor had no opportunity to deploy these strategically in the game.

The third contrast of principal interest was the interaction between intentionality (Active versus Passive) and agent (Human versus Computer). Recall that one natural prediction from the hypothesis that humans are a default target for mentalizing is that activity in brain regions associated with mentalizing will be disproportionately high for the Active-Human condition. In fact, the only brain region identified with the interaction analysis was the left frontal pole (specifically at the base of the frontal pole ~BA 11). This region has occasionally been reported in studies of mentalizing (Hynes, Baird, & Grafton, 2006; Stuss, Gallup, & Alexander, 2001), but it was not identified either by the main effect of Intentionality or by the ToM localizer in the present study. However, left frontal pole has frequently been implicated in inhibitory control and the suppression of distractions that interfere with the execution of goal-directed actions (Fuster, 2001), as well as in evaluative reasoning, in which salient but logically incorrect alternatives must be ignored (Kroger, Nystrom, Cohen, & Johnson-Laird, 2008). We propose that this activity can be understood in

terms of the hypothesis that humans are a default target for mentalizing, not because left frontal pole is involved in mentalizing per se, but because it is recruited for overcoming this processing default. As stated above, people have a basic inclination to differentiate humans and computers along the lines of intentionality (Levin et al., 2013) and to respond preferentially to stimuli and actions that are generated (or believed to be so) by humans (Stanley et al., 2010). Thus, if the default is to employ an intentional stance towards a human and an instrumental or a physical stance towards a computer, then the interaction observed in the left frontal pole may reflect the need to deploy a different stance to the one normally adopted to the interacting partner. This interpretation may also be extended to account for the deployment of the bilateral frontal pole in the Computer $_{\text{minus}}$ Human contrast by making the plausible assumption that participants have a general default to employ an intentional stance when playing a competitive game such as rock-paper-scissors which is compatible with their default for a human competitor but not their default for a computer competitor. In all, the involvement of such control regions is consistent with theoretical accounts suggesting that the attribution of intentionality and agenthood is a flexible process, and that such flexibility in the attribution of intentionality (whether to active or passive, human or computer agents) can be manipulated volitionally and even strategically (Frey, 2014), but that such strategic deployment works either with or against the default stance for a particular target or activity.

The fact that playing a human competitor only activated a subset of the regions of the "mentalizing network" activated when playing an intentional competitor may be informative about the different function of these brain regions for mentalizing. The recruitment of additional regions when playing an intentional competitor may reflect the difference between "mere mentalizing", that does not require the integration of mental states in an online activity, and the *use* or deployment of mentalizing, that systematically draws on memory for task-relevant information (e.g., what the opponent did last time; or how the identity of the

agent might determine her strategy) or resolves task-relevant conflict (between the opponent's intentions and the participant's own). These additional regions have been variably activated in a variety of theory of mind tasks (Carrington & Bailey, 2009), and appear to play a general role within the broader mentalizing network (Carrington & Bailey, 2009). For example, while there is some causal evidence that the left TPJ is as important as the rTPJ for processing mental states (Samson, Apperly, Chiavarino, & Humphreys, 2004), it appears to have a more general role in processing perspective difference for both mental and non-mental states (Perner, Aichhorn, Kronbichler, Staffen, & Ladurner, 2006). The precuneus has been implicated in processing autobiographical memory and visuospatial attention (Cavanna & Trimble, 2006), and the temporal pole is involved in face recognition and schematic knowledge of social memory (Olson, Plotzker, & Ezzyat, 2007). In addition, a closer look at activations of the rTPJ across both contrasts reveals that participants recruited both the angular and the supramarginal gyri in the Active $_{\text{minus}}$ Passive condition, and only the angular gyrus in the Human $_{\text{minus}}$ Computer condition. This is confirmed in the overlap analysis where the shared activation is in the angular gyrus. In this regard, it has been proposed that the angular gyrus is selectively involved in social cognition ("mere mentalizing", in the present study), whereas the supramarginal gyrus is more involved in attention reorienting (Kubit & Jack, 2013) which is likely to be essential for *use* of mentalizing for any practical purpose.

In conclusion, our results indicate that activation of the "mentalizing network" might be specific to mentalizing, but it is not specific to mentalizing about humans and can be activated by the mere belief that the target (human or not) is a thinking entity. Interacting with humans versus computers, however, induces activations in a more circumscribed right lateralized sub-network within the mentalizing network, consisting of the rTPJ and the anterior PCC, and which might be reflective of people's spontaneous tendency to attribute intentionality to humans. Interestingly, frontal control regions appear differentially active in

response to violation of the default stance adopted to the target, and the degree to which we readily attribute human-like abilities to the target. Together, these findings expand on earlier results from research investigating human-computer interactions in various social games (Fukui et al., 2006; Kircher et al., 2009; Krach et al., 2008; Rilling et al., 2004; Takahashi et al., 2014). They emphasize the importance of employing an orthogonal design to adequately capture Dennett's conception of the intentional stance, and consistent with Dennett's view, suggest that the same neural mechanisms are recruited for mentalizing irrespective of the nature of the target.

CHAPTER 6

AUTISM AND PSYCHOSIS TRAITS DIAMETRICALLY MODULATE THE RIGHT TEMPORO-PARIETAL JUNCTION[9]

[9] This chapter is currently under revision: Abu-Akel, A., Apperly, I.A., Wood, S.J., Hansen, P.C. Autism and psychosis traits diametrically modulate the right temporo-parietal junction.

ABSTRACT

The right temporo-parietal junction (rTPJ), subtending socio-cognitive functions such as mentalizing and domain-general computations such as attention-reorienting, is atypically activated in autism and schizophrenia spectrum disorders when performing tasks targeting these abilities. While these disorders are considered diagnostically independent, traits of both conditions can co-occur in the same individual. To date, no studies have examined the effect of co-occurring autistic and psychotic traits on rTPJ activity. Drawing on the notion that autism tendencies and psychosis proneness are dimensions of normal variation, this was investigated in neurotypical adults while performing a social competitive game known to activate the mentalizing network. Autistic and psychotic traits diametrically modulated the ventral posterior and the ventral anterior subdivisions of the rTPJ, which respectively constitute core regions within the mentalizing and attention-reorienting networks. The diametric effect within the ventral anterior rTPJ was in the opposite direction to that within the ventral posterior rTPJ. We suggest that this results from an interaction between regions responsible for higher level social cognitive processing and regions subtending domain-general attentional mechanism. The interactive effect of autism and psychosis traits implies that inter-individual differences might be better explained in terms of the relative expression of one disorder vis-à-vis the other.

INTRODUCTION

Difficulty with inferring the mental states of others ("mentalizing") is a core feature of both Autism Spectrum Disorders (ASD) and Schizophrenia Spectrum Disorders (SSD) (Chung, Barch, & Strube, 2013). Research concerned with understanding the neural system of mentalizing has identified a network of regions that primarily involves the temporo-parietal region (TPJ) and the medial prefrontal/paracingulate cortex (Abu-Akel & Shamay-Tsoory,

2011; Saxe & Kanwisher, 2003). Atypical alterations in this network have been observed independently in individuals with ASD (Ciaramidaro et al., 2014; Kana, Keller, Cherkassky, Minshew, & Just, 2009; Lombardo, Chakrabarti, Bullmore, Consortium, & Baron-Cohen, 2011) and SSD (Ciaramidaro et al., 2014; Walter et al., 2009). These atypicalities have also been observed as a function of subclinical autism (Nummenmaa, Engell, von dem Hagen, Henson, & Calder, 2012; von dem Hagen et al., 2011) and psychosis (Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010; van der Meer, Groenewold, Pijnenborg, & Aleman, 2013) traits within the healthy population. However, there is increasing empirical support for a phenotypic overlap between these spectra at the psychometric and behavioral levels in both clinical and non-clinical populations (Chisholm et al., 2015; Dinsdale et al., 2013; King & Lord, 2011; Solomon et al., 2011). This raises important questions about the nature of the relationship of these phenotypes within an individual. An alternative to the model of overlap between ASD and SSD, the diametric model (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008) conceptualizes ASD and SSD as opposite diametric conditions, such that their constituent traits should specifically not overlap to any large degree. Under this model, however, it can be predicted that co-occurring traits exert diametric effects on mentalizing abilities and corollary the neural activity subtending these abilities. Thus, assessing both autism and psychosis expressions within the same individual has important implications to understanding the nature of their association and the effect of their co-occurrence on brain and behavioral phenotypes, and more specifically, whether these phenotypes are the result of overlapping or diametric causes

To date, no studies have examined the impact of co-occurring ASD and SSD on neural activity within the mentalizing network. One approach to evaluating the impact of such co-occurrence on the neural activity within the mentalizing network is by examining its association with autistic tendencies and psychosis proneness within non-clinical populations.

This approach draws on the notion that autism tendencies and psychosis proneness are dimensions of normal variation (Baron-Cohen et al., 2001; Crespi et al., 2010b; Del Giudice, Klimczuk, Traficonte, & Maestripieri, 2014; Dinsdale et al., 2013; Nettle, 2006), with the clinical entities being at the extreme of this distribution. This approach also eliminates the confounding effects of medication or active symptomatology (Stefansson et al., 2014). To this end, we performed a functional magnetic resonance imaging study in 24 right-handed neurotypical adults while playing the well-known playground game of Rock, Paper, Scissors (RPS). This task has been shown to reliably activate the mentalizing network in a competitive context (Chaminade et al., 2012; Gallagher et al., 2002). Participants believed they were playing against four possible opponents: (1) an *active human* agent who was a skilled RPS player, (2) a *passive human* agent who followed a predetermined response script (i.e., the player simply executed the moves that were prepared in advance), (3) an *active intelligent computer* program, and (4) a *passive computer* program that followed a predetermined response script. These four conditions thus comprised a 2x2 experimental design with one factor being the human vs. computer opponent and the other factor being the element of implied agency from the opponent (active vs. passive). Psychosis proneness was assessed using the positive scale of the Community Assessment of Psychic Experiences Questionnaire (Stefanis et al., 2002) and autism tendencies were assessed using the Autism Spectrum Quotient (Baron-Cohen et al., 2001). The assessment of positive schizotypy rather than the general construct of schizotypy which comprises both negative and positive symptoms is based on evidence for autism-positive schizotypy axis in the non-clinical population (Dinsdale et al., 2013), and that negative symptoms do not reliably discriminate between the ASD and SSD (Kastner et al., 2015; Spek & Wouters, 2010). We thus asked whether variation in co-occurring autism and positive psychosis spectrum traits has an impact on the neural activity of core regions within the mentalizing network of neurotypical brains.

METHODS AND MATERIALS

Participants

24 right-handed, English proficient healthy adults (5 Males; 19 Females; Mean Age ± SD = 21.21±4.21) participated in the study. Participants did not have a history of psychiatric illness, epilepsy, neurological disorders, brain injury as well as current alcohol or substance abuse problems. The study was approved by the University of Birmingham Research Ethics Committee, and written informed consent was obtained from all participants.

Materials and procedures

Psychosis proneness, assessed using the positive scale of the Community Assessment of Psychic Experiences (CAPEp) Questionnaire (Stefanis et al., 2002), autism tendencies, assessed using the Autism Spectrum Quotient (AQ) Questionnaire (Baron-Cohen et al., 2001), English reading proficiency, assessed with the Test of Irregular Word Reading Efficiency (TIWRE) (Reynolds & Kamphaus, 2007) and the Test of Word Reading Efficiency (TOWRE) (Torgesen et al., 1999) questionnaires, and handedness, ascertained with the modified Annett Handedness Questionnaire (Annett, 1972), were administered to 27 participants, on average 7-10 days prior to the scanning session. Of the 27, 24 were scheduled for the scanning session during which they performed two tasks. The three participants could not attend the scanning session due to scheduling conflicts. The first is a computerized version of the Rock, Paper, Scissors game. The second is Hartwright et al.'s (Hartwright et al., 2012) variant of Saxe and Kanwisher's (Saxe & Kanwisher, 2003) theory of mind (ToM) functional localizer task. At the end of the scanning session, all participants went through a debriefing interview.

The rock, paper, scissors (RPS) task

In this task, participants are required to predict the moves of their opponent in order to win. The game has the following simple rules: Rock beats scissors, paper beats rock, and scissors beat paper. The winner of each round is awarded 1 point. A no-response results in an automatic win for the opponent, and identical moves results in a draw and no points are awarded. Here we orthogonally manipulated the intentional stance during the game in such a way that the participants are led to believe that they are playing under four conditions: (1) against an *active* human agent who is a skilled RPS player, (2) a *passive* human agent who is followed a predetermined script, (3) an *active* intelligent computer program (called AIRPS) that was capable of analyzing the participant's strategy, and (4) a *passive* computer program that followed a predetermined response script.

Participants were cautioned not to use a stereotyped strategy and to play competitively with the intention of beating their opponent. Feedback was provided during the scan sessions as to how well the participant was scoring at the end of each block of ten rounds of the game and a summary of the results at the end of each fMRI run. Positive scoring and effort were rewarded with a prize of £10 for the highest performing participant overall at the end of the study. Before each one of the four conditions, participants were provided with on-screen instructions to remind them of what they are required to do and of the opponent against whom they would be playing. To reinforce the impression that the participant was truly playing against a 'human' opponent, a 3% fallibility 'no-response' measure was embedded during the human conditions.

Crucially, unbeknownst to the participants, the game was always played against a computer program generating moves entirely at random. The design ensured that the only difference across the conditions was the perceived identity of the participant's opponent under the various conditions. To check participants' perception of their opponents, a

debriefing procedure was utilized after the scanning session during which participants were asked to recount how they understood and experienced these conditions. None of the participants expressed doubt regarding the identity of the four opponents.

The RPS experiment consisted of 5 fMRI runs, each lasting 440s per run (~40mins total). Each fMRI run consisted of 4 blocks, representing the four conditions of interest. The sequence of opponents was chosen from 8 predetermined player-sequences (chosen from the 24 possible sequences) such that on each sequence the human and the computer opponents were presented in alternating order. The sequences the participants' played, in each of the 5 fMRI runs, were selected in a pseudorandom order.

Each block was preceded by a 10s period during which the instructions were displayed, and followed by a 30s rest period. During each block the participant played 10 trials against one of the four possible opponents. Response selections (i.e., rock, paper or scissors) were made using a button box with three active buttons that was placed in the participant's left hand. See Figure 6.1 for a schematic representation of stimuli presentation and timing during each trial. All participants went through a practice session of 2 blocks outside the scanner. The experiment was presented using Presentation (Neurobehavioral Systems, CA), which also recorded the behavioral data (button pressed and reaction time).

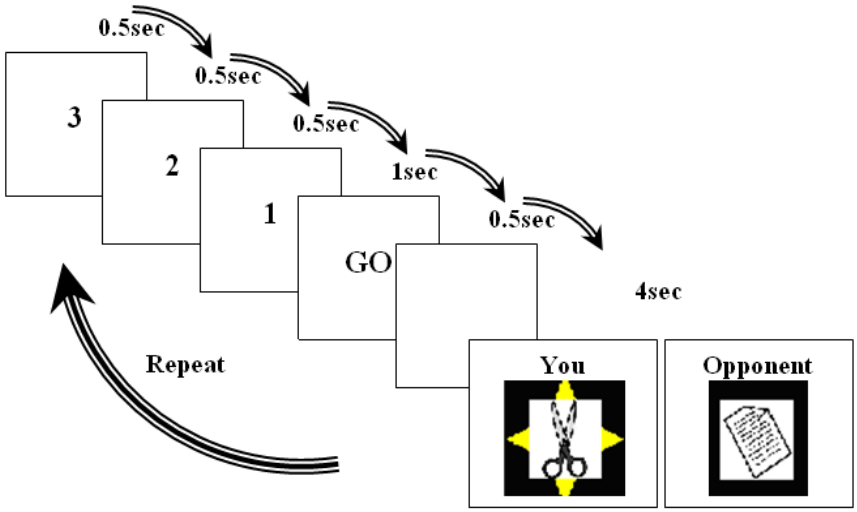

Figure 6.1. Each trial began with a countdown 3, 2, 1, in 0.5s intervals, followed by 'GO' during which the participants make their moves. The 'GO' was present for 1s followed by a 0.5s blank screen. The results screen is then displayed for 4s indicating the moves drawn by both players and the outcome. Winning move is displayed with a yellow star.

The Community Assessment of Psychic Experiences (CAPE) Questionnaire

This self-report questionnaire is based on the Peters et al. Delusions Inventory-21 (PDI-21) (Peters et al., 1999) and consists of 42 items measuring the presence of *positive* psychotic experiences (20 items), *negative* psychotic experiences (14 items), and *depressive* experiences (8 items) that an individual may have experienced over the last 12 months (Stefanis et al., 2002). The occurrence of these symptoms is reported on a likert frequency scale from 1 (never) to 4 (nearly always), and the associated distress on a scale ranging from 1 (not distressed) to 4 (very distressed). Cronbach's α for this scale in this study is .89, which indicates high internal consistency. For current purposes, the 20-item CAPE positive scale is used as a measure of psychosis proneness. The internal consistency of this scale in this study is good (Cronbach's α = .75), and falls within the range of values reported in other studies within the general population (Lin et al., 2011). In the current study, participants had a mean score of 25.28 (Range: 20-32; SD=±3.57).

The Autism Spectrum Quotient (AQ) Questionnaire

This self-report questionnaire consists of 50 items that measure the presence of traits associated with the autistic spectrum within the general population(Baron-Cohen et al., 2001). Each item is given a score of 0 or 1. Higher scores indicate the presence of greater autistic tendencies. The AQ's internal consistency in this study is good (Cronbach's $\alpha = .81$), and is comparable to the values reported in other studies (Austin, 2005). In the current study, participants had a mean score of 15.49 (Range: 3-31; SD=±6.65). The association of the AQ with the CAPE positive scale was non-significant (r=.28, p=.19) (see Appendix 3, Figure 1).

fMRI data acquisition and analysis

Data were acquired in a single scanning session using a 3T Philips Achieva scanner. 176 T2*-weighted standard echo planar imaging (EPI) volumes were obtained in each of the RPS task runs, using a 32 channel head coil. Parameters used to achieve whole brain coverage are as follows: TR=2.5s, TE=35ms, acquisition matrix = 80 x 80, flip angle =83°, isotropic voxels 3x3x3 mm^3, 42 slices axial acquisition obtained consecutively in a bottom-up sequence. Using the same parameters, 71 EPI volumes were acquired for each block of the localizer task. A T1-weighted scan was then acquired as a single volume at higher spatial resolution as a 3D TFE image (matrix size 288x288, 175 slices, sagittally acquired and reconstructed to 1x1x1 mm^3 isotropic voxels. TE =3.8ms. TR = 8.4 ms).

Preprocessing and statistical analyses of the data were performed using the FMRIB software library (FSL version v.5.0.6; FMRIB, Oxford, www.fmrib.ox.ac.uk/fsl). For both experiments, initial preprocessing of the functional data consisted of slice timing correction, and motion correction (MCFLIRT). The blood oxygen level dependent (BOLD) signals were high-pass filtered using a Gaussian weighted filter to remove low-frequency drifts in the bold signal. Spatial smoothing of the BOLD signal was performed using a 5mm full-width-half-

maximum kernel. The functional data were registered to their respective structural images and transformed to a standard template based on the Montreal Neurological Institute (MNI) reference brain, using a 6-DoF linear transformation (FLIRT).

RPS task experiment analysis

Playing against a computer or a human, with either agency or by following a script, provided the four baseline conditions. These four conditions comprised a 2x2 ANOVA experimental design with factor 1 being the human vs. computer opponent and factor 2 being the element of implied agency from the opponent (active vs. passive). Condition regressors were convolved with the canonical hemodynamic response function within a general linear model framework (GLM). A high-pass filter with a cut-off of 105s was used. Motion parameters were treated as regressors of no interest in order to account for unwanted motion effects. Session data were aggregated per participant using a second level fixed effects model. Third level modelling was used to aggregate the data across participants in a 2x2 repeated measures ANOVA with Active vs. Passive and Human vs. Computer as within subjects factors, employing a mixed effects analysis with cluster based thresholding at $Z > 2.3$, $pcorr < 0.05$. An overlap analysis between the thresholded data ($Z > 2.3$, $p$corr < 0.05) for the Human > Computer and the Active > Passive contrasts was then conducted to identify shared activations across the two thresholded contrasts. The analysis was conducted with FSL's *easythresh* function (Nichols et al., 2005).

Regions of Interest (ROI) analysis

ROI analysis focused on the rTPJ and the paracingulate cortex since only these two regions were active in both the Active > Passive as well as in the Human > Computer contrasts during the RPS task as revealed by the overlap analysis. Masks for these two regions were

generated from the ToM localizer task (Hartwright et al., 2012). For each of these ROIs, the mean percentage signal change in each of the four RPS experimental conditions was extracted from the aggregate data of each participant across the five runs (i.e., the 24 second-level models) using FSL Featquery (www.fmrib.ox.ac.uk/fsl/feat5/featquery.html).

Statistical analysis

To evaluate the association of autism tendencies and psychosis proneness on the hemodynamic response of the region, we utilized Generalized Linear Models where the Active vs. Passive and Human vs. Computer were entered as fixed factors, and the participants' standardized Z scores on the AQ, CAPEp and their interaction were entered as covariates. Interaction terms were probed by depicting simple regression lines using the method by Hayes and Matthes (Hayes & Matthes, 2009) whereby the effect of one predictor is examined at the mean, one standard deviation below the mean and one standard deviation above the mean of the other predictor. It is important to note, that these are arbitrary cut-off points and are used here in keeping with the tradition of unpacking interactions using this method.

RESULTS

The overlap analysis between the thresholded data ($Z > 2.3$, $p\text{corr} < 0.05$) for the Human > Computer and the Active > Passive contrasts revealed shared activations in the paracingulate [-4, 50, 20] and the rTPJ [58, -52, 28]. Masks for these two regions were generated from a Theory of Mind (ToM) Localizer Task (Hartwright et al., 2012; Saxe & Kanwisher, 2003) (see Figure 6.2).

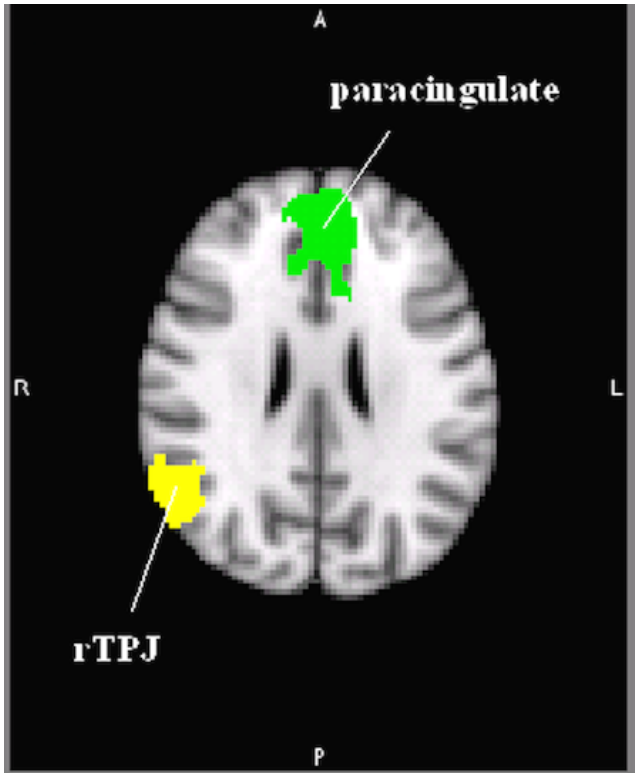

Figure 6.2. Masks for the overlapping regions between the Human > Computer and the Active > Passive contrasts are generated from the Theory of Mind Localizer Task. Coordinates of the mask for the paracingulate cortex (in green) are [-4, 50, 20] and for the rTPJ (in yellow) are [58, -52, 28].

To evaluate the impact of autism tendencies and psychosis proneness on the hemodynamic response of the paracingulate cortex and the rTPJ, we first investigated, using Generalized Linear Models, the hemodynamic response of the paracingulate as a function of the participants' standardized Z scores on the AQ, CAPEp and their interaction. The omnibus test showed that the overall model was non-significant (χ^2 =9.92, df=6, p=.13). However, when the data for the rTPJ were subject to the same analysis, the overall model was significant (χ^2=19.62, df=6, p=.003, R^2=.19). The model's parameter estimates indicated that activity within the rTPJ was negatively associated with AQ scores (β(se)=-.070(.028), df=1, χ^2=6.54, p=.011), and positively with both the CAPEp scores (β(se)=.102(.027), df=1, χ^2=13.74, p<.001) and the interaction term (β(se)=.077(.022), df=1, χ^2=11.86, p=.001) (see Figure 6.3 and Appendix 3, Table 1).

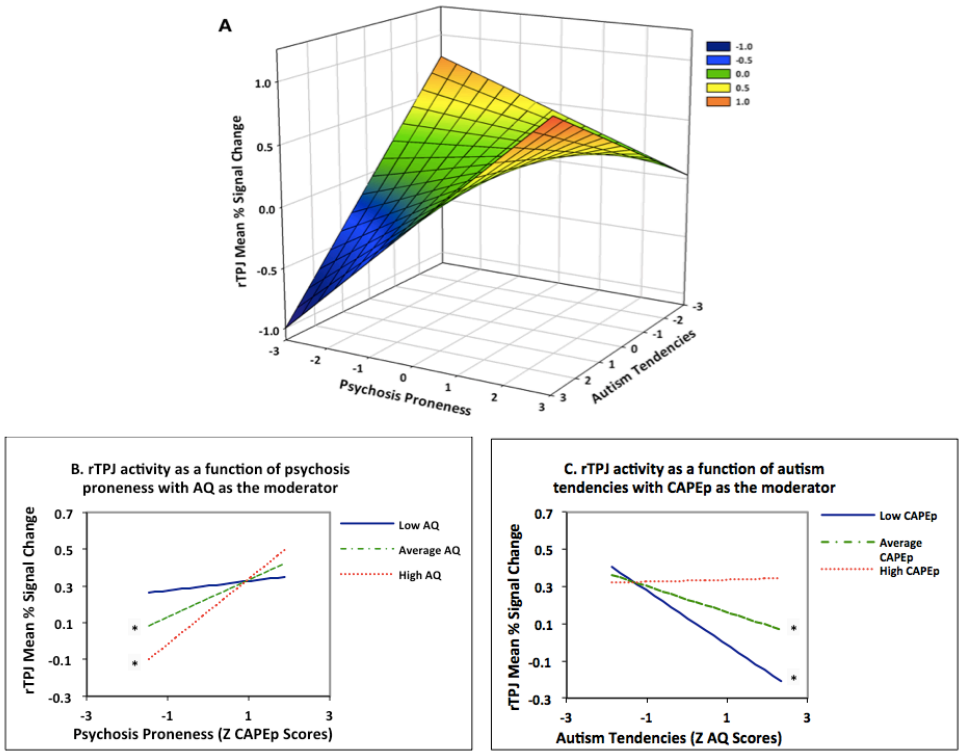

Figure 6.3. (A) 3-D representation of the interactive effect of autism tendencies and psychosis proneness on mean percent signal change of the rTPJ. (B) Visualizes the association between psychosis and rTPJ activity by plots of simple regression lines with low (-1 SD), average, and high (+1 SD) AQ scores as moderators, showing an increase in the positive effect of psychosis proneness on rTPJ activity with increasing autism tendencies. (C) Visualizes the association between autism tendencies and rTPJ by plots of simple regression lines with low (-1 SD), average, and high CAPEp (+1 SD), showing a decrease in the negative effect of autism tendencies on rTPJ activity with increasing psychosis proneness. Asterisk = *p*-value <.05.

As can be seen from Figure 6.3A, rTPJ activity is greater in psychosis-prone individuals (i.e., those with high psychosis scores and low AQ scores) compared to autism-prone individuals (i.e., those with low psychosis scores and high AQ scores). Intriguingly, however, the rTPJ activates to a similar degree in individuals presenting with high scores as well as in individuals presenting with low scores on both scales. Thus, in order to examine if rTPJ activity is modulated by the relative expression of psychosis vis-à-vis autism, the participants' psychosis bias was calculated by subtracting their z-normalized AQ scores from

their z-normalized CAPEp scores. A regression analysis confirmed that the Psychosis-Bias scores positively predicted rTPJ activity (β(se)=.095(.022), df=1, χ^2=19.49, p<.001).

Next, we probed the interaction term using the method by Hayes and Matthes (2009) described above. We see that the relationship between psychosis proneness and rTPJ activity (Figure 6.3B) was significant when the AQ scores were at the mean (β=0.102, p=0.002) as well as when they were high (+1 SD) (β=0.177, p<.001), but not when they were low (-1 SD) (β=0.026, p=0.54). Conversely, the relationship between autism tendencies and rTPJ activity (Figure 6.3C) was significant when the CAPEp scores were low (-1 SD) (β=-0.146, p=0.003) as well as when they were at the mean (β=-0.076, p=.038), but not when they were high (+1 SD) (β=0.006, p=0.89). This pattern suggests that activity within the rTPJ is diametrically modulated by autism tendencies and psychosis proneness.

However, the precise role of the rTPJ has been the subject of competing hypotheses. Indeed, the rTPJ, in addition to its role in mentalizing, has been implicated in saliency, attention-reorienting and self-other distinction (Corbetta et al., 2008; Decety & Lamm, 2007). Consequently, it is not clear whether the rTPJ is a shared neural basis for all of these functions, or whether it consists of subregions supporting specific functions (Carter & Huettel, 2013; Corbetta et al., 2008; Decety & Lamm, 2007; Mars et al., 2012). In this regard, Mars and colleagues (Mars et al., 2012), using diffusion-weighted imaging tractrography-based parcellation, have shown that the rTPJ (delineated to include all areas labeled as TPJ in previous studies) consists of at least 3 subregions with distinct pattern of functional connectivity. As can be seen from Figure 6.4A, these subregions consist of a dorsal subregion (rdTPJ), largely corresponding to the inferior parietal lobule, and a ventral subregion, which is further subdivided into a posterior (rvpTPJ) and an anterior (rvaTPJ) subregions. The rdTPJ is functionally connected with a network including the lateral anterior PFC and forms part of the Task Positive Network. The rvpTPJ and the rvaTPJ are respectively functionally

connected with the mentalizing and the attention-reorienting networks. The association of the rvpTPJ and the rvaTPJ with mentalizing and attention-reorienting is consistent with a meta-analysis of 70 functional neuroimaging studies showing that, on average, attention-reorienting activates anteriorly and ToM processing posteriorly (Decety & Lamm, 2007), as well as with more recent studies investigating the *territorial* integrity of the rTPJ (Bzdok et al., 2013; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). Note that the rvpTPJ, as defined in Mars et al. (2012), overlaps considerably with the region within which we conducted our analyses in Figure 6.3 above (see Figure 6.4B).

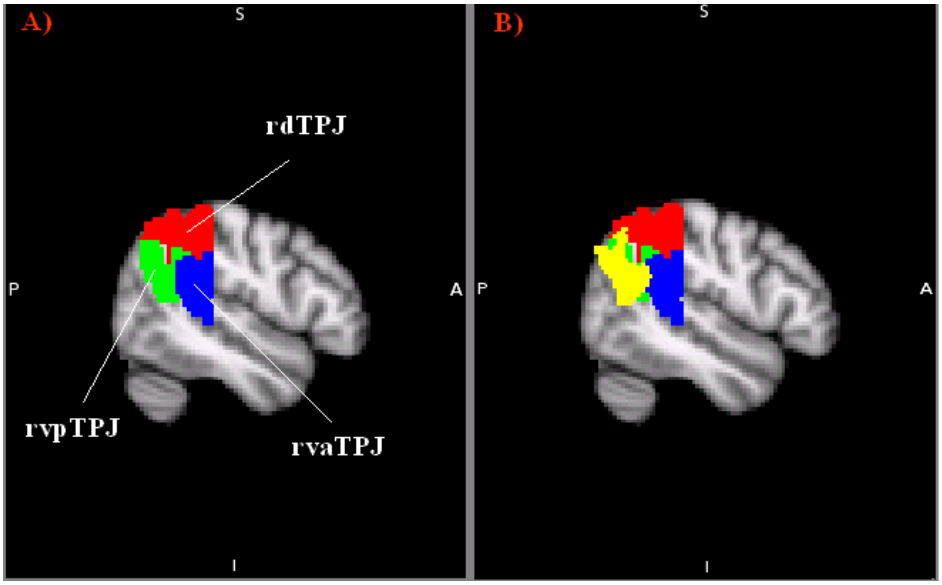

Figure 6.4. (A) Mars et al.'s (Mars et al., 2012) parcellation of the right TPJ into dorsal (center of gravity [49, -46, 46]) (rdTPJ), ventral posterior [54, -55, 26] (rvpTPJ) and ventral anterior [59, -37, 30] (rvaTPJ) subdivisions. Masks were obtained from *www.rbmars.dds.nl/CBPatlases.htm*[10] (B) An overlay of the rTPJ (in yellow), defined by the ToM localizer task, over the rTPJ, as delineated by Mars et al., shows that our localized rTPJ [56, -64, 30] significantly matches the rvpTPJ, with minimal overlaps with the rdTPJ and the rvaTPJ. Regions are superimposed on a sagittal section, x=20.

To shed light on this debate, we utilized the masks from Mars et al. to further examine the neural activity of the rdTPJ and rvaTPJ as a function of autism tendencies and psychosis

[10] We thank Rogier Mars and Matthew Rushworth for use of masks.

proneness. The omnibus test for the rdTPJ was non-significant (χ^2 =9.80, df=6, p=.13), but significant for the rvaTPJ (χ^2 =17.03, df=6, p=.009, R^2=.16). Parameter estimates indicated that rvaTPJ activity was negatively associated with CAPEp scores (β(se)=-.052(.018), df=1, χ^2=8.20, p=.004) and positively with the interaction term (β(se)=.073(.015), df=1, χ^2=24.53, p<.001). The association with the AQ scores was negative but non-significant (β(se)=-.013(.020), df=1, χ^2=.38, p=.54) (see Figure 6.5 and Appendix 3, Table 2).

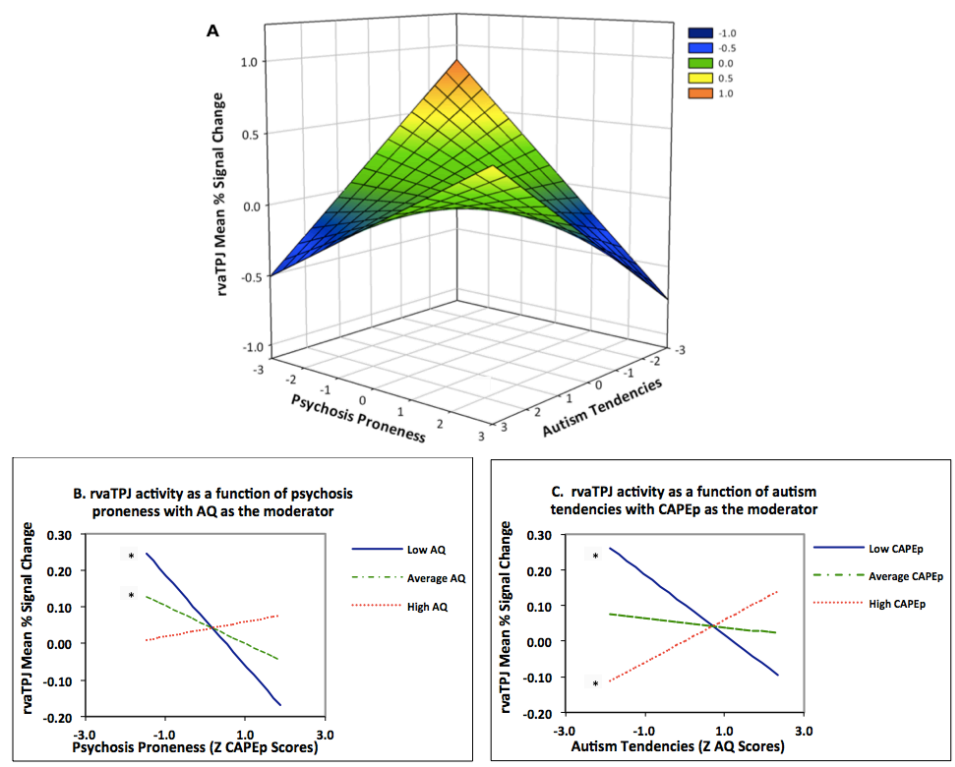

Figure 6.5. (A) 3-D representation of the interactive effect of autism tendencies, psychosis proneness on mean percent signal change of the rvaTPJ. (B) Visualizes the association between psychosis and rvaTPJ activity by plots of simple regression lines with low (-1 SD), average, and high (+1 SD) AQ scores as moderators, showing a diminishing of the negative effect of psychosis proneness on rvaTPJ activity with increasing autism tendencies. (C) Visualizes the association between autism and rvaTPJ by plots of simple regression lines with low (-1 SD), average, and high CAPEp (+1 SD), showing a diminishing of the negative effect of autism tendencies on rvaTPJ activity with increasing psychosis proneness. Asterisk = *p*-value <.05.

In contrast to the pattern of activation we observed in the rvpTPJ (Figure 6.3A), autism-prone individuals (i.e., those with high AQ scores and low psychosis scores) compared to psychosis-prone individuals (i.e., those with low AQ scores and high psychosis scores) tend to have higher rvaTPJ activity (Figure 6.5A). Intriguingly, here too, we see that the rvaTPJ activates to somewhat a similar degree (albeit to a lesser degree of symmetry) in individuals presenting with high scores as well as in individuals presenting with low scores on both scales. In contrast to the rvpTPJ, a regression analysis revealed that the Psychosis-Bias scores were negatively associated with the activity of the rvaTPJ ($\beta(se)=-.056(.018)$, $df=1$, $\chi^2=9.26$, $p=.002$).

Furthermore, when probing the interaction between the AQ and CAPEp scores, the positive relationship between psychosis proneness and rvaTPJ (Figure 6.5B) was significant when the AQ scores were low ($\beta=-0.124$, $p<0.001$) as well as when the AQ scores were at the mean ($\beta=-0.052$, $p=.048$), but non-significant when they were high (+1 SD) ($\beta=0.020$, $p=0.50$). Conversely, there was a negative relationship between autism tendencies and rvaTPJ (Figure 6.5C) when the CAPEp scores were low (-1 SD) ($\beta=-0.084$, $p=0.030$), none at the mean ($\beta=-0.012$, $p=.64$), and trending towards a positive relationship when the CAPEp scores were high (+1 SD)($\beta=0.060$, $p=0.063$), but which becomes significant ($p<.05$) in individuals scoring above a Z value of 1.056 (which roughly corresponds to a score of 29 on the CAPEp scale). This pattern of activity suggests that activity within the rvaTPJ is also diametrically modulated by autism tendencies and psychosis proneness, but in different, and largely opposite pattern when compared to the rvpTPJ (Figure 6.3).

DISCUSSION

The observed diametric influences of autism tendencies and psychosis proneness on the neural activity within the ventral posterior (mentalizing) and anterior (attention-reorienting)

rTPJ is consistent with the diametric model positing that autism and psychosis spectrum disorders are etiologically and phenotypically diametrical exerting opposing influences on activity and behavior (Abu-Akel & Bailey, 2000; Abu-Akel et al., 2015; Crespi & Badcock, 2008; Crespi et al., 2010). Thus we propose that the diametric modulation of the rvpTPJ reflects the neural effort to balance the tendency of psychosis to lead to overmentalizing and autism to undermentalizing (Abu-Akel & Bailey, 2000; Ciaramidaro et al., 2014; Crespi & Badcock, 2008; Crespi et al., 2010). Indeed, mentalizing studies have largely observed overactive rTPJ in psychosis spectrum disorders (Bara, Ciaramidaro, Walter, & Adenzato, 2011; Ciaramidaro et al., 2014; Walter et al., 2009; Wible, 2012) and contrastingly an underactive rTPJ in autism spectrum disorders (Bara et al., 2011; Ciaramidaro et al., 2014; Lombardo et al., 2011).

This neural pattern was not observed in all studies. For example, studies show a positive association between AQ scores and rTPJ activity (Nummenmaa et al., 2012; von dem Hagen et al., 2011). However, the positive correlation found in the Nummenmaa et al. study was during an attentional/gaze perception task, and that of the von dem Hagen et al. study was in a region whose coordinates [52, -42, 12] fall within the rvaTPJ, both of which are consistent with our current finding showing that activity in the attentional rvaTPJ is positively associated with AQ scores. It is noteworthy that the AQ scores in the Nummenmaa et al. study also correlated positively with the supramarginal gyrus, which constitutes part of the rvaTPJ as defined in our study. With respect to psychosis proneness, both van der Meer et al. (2013) and Modinos et al. (2010) detected no differences between low versus high psychosis-prone groups in the rTPJ when performing mentalizing tasks. However, dividing the participants into low and high groups is not amenable to assessing the effect of individual differences on the degree of neural activation.

Similarly, the diametric activation of the rvaTPJ (Figure 6.5) appears to reflect the neural effort to balance the inability to filter unimportant and distracting information associated with psychosis and the tendency for increased focus of attention associated with autism. This interpretation is consistent with findings showing that deactivation in this region reflects the filtering of irrelevant and distracting information, and that such deactivation ceases once a target has been detected (Shulman, Astafiev, McAvoy, d'Avossa, & Corbetta, 2007). Although attention re-orienting was not measured behaviorally in our study, we tested whether the autism-related up-regulation of the rvaTPJ might reflect increased focus of attention. A regression analysis showed that activity of the rvaTPJ was only positively associated with the attention-switching subscale of the AQ questionnaire, where higher scores reflect stronger focus of attention ($\beta(se)=.069(.025)$, df=1, $\chi^2=7.77$, p=.005) (Appendix 3, Table 3). This finding is consistent with Nummenmaa et al. (2012) who also reported positive association between the attention-switching subscale and rTPJ activity while performing an attentional/gaze perception task. It is important to note, that the attention-switching subscale was not associated with rvpTPJ activity (($\beta(se)=.032(.035)$, df=1, $\chi^2=0.85$, p=.36). Taken together, we propose that higher psychosis-proneness leads to an increase in the availability of information due to reduced information filtering (reflected in deactivation in rvaTPJ) and consequently greater effort when trying to mentalize with this information (reflected in greater rvpTPJ activity). These consequences of psychosis-proneness are countered by the relative expression of the autistic trait associated with attentional focus, which restricts the amount of information available for mentalizing in the rvpTPJ. This interpretation is consistent with the opposing domains hypothesis positing reciprocal interaction between regions involved in social cognition and regions involved in attentional processing (Jack et al., 2012; Kubit & Jack, 2013).

Based on the strong interactive effect between autism and psychosis expressions in the rTPJ, we suggest that such inter-individual variation within and across disorders can be accounted for in terms of the relative expression of one disorder vis-à-vis the other. However, given that our findings are based on the relative expression of autism and psychosis traits among neurotypical adults, a further critical step is to examine whether these findings generalize to their respective clinical entities. Nonetheless, the impact of these sub-threshold clinical traits on neural functioning in a manner similar to what has been observed in patients with these disorders suggests that neural abnormalities are not necessarily a consequence of the disorders, and raises the possibility that an important difference between patients and non-patients is in the relative expression of autism and psychosis traits. Our findings thus provide a framework that could reconcile discrepant results such that hypo- or hyper-activation in either disorder may be due to failure to capture the diametric influence of the other disorder. Additionally, the effect of individual differences in autism and psychosis traits in neurotypicals on neural activity raise concerns regarding hitherto findings reported in studies comparing clinical and non-clinical groups. Might differences (or lack thereof) between clinical and healthy controls be confounded by the relative expression of autism and psychosis traits in 'healthy' controls? That is, it is reasonable to assume that the extent of the difference between the healthy and the clinical populations is a function of the extent of subclinical expressions in the healthy group.

Our study is the first to show that the postulated diametric modulation of autism tendencies and psychosis proneness on behavior and performance are detectable at the neural level in a region that is a core component of social functioning. The association of the neural response in the socio-cognitive and attention-reorienting networks with the extended autism and psychosis spectra in the neurotypical population further suggests that the assessment of both spectra in the "control group" could have important consequences for establishing

baseline measures for the assessment of behavior and brain phenotypes in the clinical groups. Furthermore, the contrastive modulation of the ventral anterior versus the posterior rTPJ underscores the distinct functionality of these subdivisions (Corbetta et al., 2008; Mars et al., 2012; Scholz, Triantafyllou, Whitfield-Gabrieli, Brown, & Saxe, 2009), and provides an insight for the debate surrounding the functional link between regions responsible for higher level social cognitive processing and regions associated with domain-general attentional processes.

CHAPTER 7

GENERAL DISCUSSION

INTRODUCTION

The association between autism and psychosis is an area of considerable interest and debate, particularly in light of emerging evidence questioning the long-standing consensus of autism and psychosis spectrum disorders as mutually exclusive conditions. One set of evidence suggests that autism and psychosis share many phenomenological similarities that can be traced to common neurodevelopmental origins or genetic predispositions. A second set of evidence suggests that autism and psychosis exert opposite effects on phenotypes that can be traced to diametric genetic and biological mechanisms. These models and the evidence supporting them present significant conceptual difficulties to the current perception of autism and psychosis as distinct categorical conditions, but studies that systematically examine their merit are lacking.

To reconcile such conceptual difficulties, autism and psychosis are regarded in this thesis as dimensional conditions that follow a standard distribution curve with most individuals carrying some liability for autism and psychosis, and only a small fraction of the population has a liability that exceeds the clinical threshold. By adopting the view of autism and psychosis as dimensional conditions, the thesis presented a heuristic framework that allowed for the simultaneous assessment of the independent, overlapping and diametric models by (1) simultaneously quantifying autism and psychosis expressions within the same individual, and (2) by examining their concurrent effect on endophenotypes that are known to affect both individuals with autism and psychosis.

To this end, the thesis has presented a series of studies exploring the interactive effect of autism tendencies and psychosis proneness on perspective-taking and saliency-based selection in healthy individuals, using a variety of techniques and methodologies. These abilities represent core features of social interaction and are severely disrupted in both autism and psychosis. In addition, the thesis sought to investigate whether this interactive effect is

recoverable at the neuronal level. Overall, the findings from the series of studies suggest that autism and psychosis have a significant interactive effect on neuronal and behavioral phenotypes. This interactive effect has important implications to our current understanding of the effect of autism and psychosis on outcome measures, the nature of their association and more generally the future of psychiatry.

In the following pages, I first thematically summarize the main empirical findings of the thesis and their implications to understanding perspective-taking and saliency in both autism and psychosis. Second, I discuss the clinical relevance of the methodological approaches and findings. Third, I discuss limitations of research and future directions. Finally, I conclude with comments highlighting the importance of the simultaneous assessment of autism and psychosis to understanding their relative contribution to behavioral and neuronal phenotypes. However, I would like to note that since the empirical chapters were written as self-contained papers, I took the liberty to go beyond the empirical findings in the interest of underscoring the potential of the research approach undertaken in this thesis and the future research opportunities it offers.

THE INTERACTIVE EFFECT OF AUTISM AND PSYCHOSIS

The interactive effect of autism and psychosis on resolving conflicting information

Autism and psychosis are conditions of social and cognitive dysfunctions. Perspective-taking abilities and the ability to attend towards (or away from) salient information are important for social communication and functioning. In interactive contexts, for example, communication is likely to breakdown if one fails to realize perspectival difference, or act on this information in timely manner. Similarly, social functioning difficulties can arise due to an inability to suppress or filter out distractors. While there is considerable evidence of impairments in both

autism and psychosis, the evidence is also rather inconsistent, perhaps because it is uncommon to assess both autism and psychosis in the same individual.

Chapter 2 and 3 and Chapter 4 were aimed at assessing the interactive effect of autism and psychosis on two separate domains, i.e., perspective-taking and saliency-based selection. However, while separate, they share a fundamental aspect, which is one's ability to resolve conflicting information en route to achieving a specific goal. As such, Chapters 2-4 present convergent evidence suggesting that the ability to resolving conflicting information in both the sociocognitive and attentional domains are sensitive to inter-individual differences in the expression of autism and psychosis traits. More important, these studies reveal consistent evidence suggesting that autism tendencies and psychosis proneness interactively improve one's ability to resolving conflicting information within these domains. This is demonstrated by showing that the interaction is associated with a reduction in the probability of making perspective-taking errors (Chapter 2), increasing the efficiency of perspective-taking (Chapter 3), and in increasing the efficiency of detecting a target in the presence of salient distractors (Chapter 4).

An analysis of this interaction suggests that the effect engendered by the expression of one condition (e.g., psychosis) on the outcome measure (e.g., saliency cost) is dampened by the relative expression of the other condition. If autism and psychosis have contrasting effects on an outcome measure, this leads one to postulate that the ability to resolve conflicting information might be due to the diametric modulation of autism and psychosis on complementary/interacting mechanisms. With respect to the perspective-taking task, the paradigm itself cannot distinguish between errors that are attributable to autism tendencies versus those attributable to psychosis proneness. However, one can imagine that the benefits borne out of the interaction between autism and psychosis might be associated with the reconciliation or a tradeoff between two contrasting mentalizing styles specific to autism and

psychosis—autism is associated with the inability to represent mental states, whereas psychosis is associated with tendencies to overattribute mental states (Abu-Akel & Bailey, 2000; Crespi & Badcock, 2008; Fretland et al., 2015; Frith, 2004). Similarly, in the saliency tasks, one can imagine that the attenuation of interference from salient distractors is the result of a tradeoff between the tendencies for attentional focus in autism (Baron-Cohen et al., 2001; Ronconi, Gori, Ruffino, Molteni, & Facoetti, 2013) and the tendency to overswitch in psychosis (Yogev et al., 2003; Yogev et al., 2004). In this context, attentional focus may enable greater distractor suppression (hence less interference) and overswitching may be associated with the *irresistible* tendency to attend to the salient distractor (hence greater interference). The findings presented in Chapter 6 provide some evidence in favor of this argument. There, I presented evidence suggesting that the attentional subdivision of the rTPJ is contrastively modulated by autism and psychosis tendencies, wherein activity decreases as a function of psychosis, and increases as function of autism and particularly attentional focus. These patterns of activations correspond to the information gating (or filtering) function that has been proposed for this region (Shulman et al., 2007), where deactivations correspond with the gate being open and activations with the gate being closed.

Coming full circle, one can thus see how the interactive effect of autism and psychosis on attentional subdivision of the rTPJ can affect the neuronal activity of the socio-cognitive subdivision of the rTPJ. Namely, the responsivity of the sociocognitive rTPJ would depend on the degree to which the attentional subdivision of the rTPJ allows for already represented models to be updated (cf. (DiQuattro, Sawaki, & Geng, 2014; Geng & Vossel, 2013)). This begs the question as to whether the social effects are indeed driven by attention effects. While not definitive, there is evidence that some theory of mind paradigms activate the ventral attentional system (i.e., the TPJ and the inferior frontal gyrus (IFG)) (Hartwright et al., 2012; van der Meer, Groenewold, Nolen, Pijnenborg, & Aleman, 2011; van der Meer

et al., 2013)—the same system that is involved in saliency-based selection (Corbetta et al., 2008; DiQuattro & Geng, 2011; Geng & Mangun, 2011). For example, Hartwright et al. (2012) showed that the IFG was recruited in the service of false belief reasoning during the high inhibition condition in which participants needed to reason about beliefs that were false compared to reasoning about beliefs that were true (the low inhibition condition). Similarly, van der Meer et al. (2013) have shown, compared to low psychosis-prone individuals, greater activation in the IFG in high psychosis-prone individuals when performing a theory of mind task that required the inhibition of the self-perspective. However, causality cannot be inferred from these studies, and therefore future work is needed to determine the causal relationship between the attention and the mentalizing neural networks, and the way this relationship can be affected by the relative expression of autism vis-à-vis psychosis.

Following from the above discussion, it is feasible thus to propose that these contrasting information processing styles represent two poles of irregularities across the autism and psychosis spectra and which appear to converge in a compensatory manner, particularly in individuals with balanced expression of autism and psychosis. However, the equifinality of performance in individuals with low versus high balanced expressions of autism and psychosis is not without cost. By systematically tracking the eye-movements of participants whilst performing a more sensitive version of the perspective-taking task (Chapter 3), the high balanced group performed at increased processing cost. The difference between low and high balanced individuals was also observed in the activation of the anterior rTPJ which was activated less in the high balanced individuals (see Chapter 6, Figure 6.5). These findings are important as they suggest that having high expressions of both autism and psychosis comes with certain liability. In addition, these findings give further credibility to the robustness of the measures used to quantify the expression of autism and psychosis, in

that scoring low or high on both questionnaires is not simply a response bias by participants who indiscriminately endorse (or not) questionnaire items.

Collectively, these findings have important implications for research investigating socio-cognitive and attentional abilities within both the healthy and the clinical populations. As demonstrated in this thesis, a substantial source of the variance in perspective-taking and saliency-based selection can be traced to inter-individual variations in the expression of the autism and psychosis. While these of course are not the only variables that explain the effects observed here, they have important implications for research assessing these domains within the clinical populations in at least two respects. First, the true state of affairs in individuals with autism or psychosis might be masked by the relative expression of the unmeasured condition. Second, the differences between clinical and non-control groups on a particular outcome measure is likely to vary across studies, as the magnitude of the difference is likely to be susceptible to the relative expression of these conditions within both the healthy and clinical groups. The development of sensitive measures that can capture continuously the whole range of autism and psychosis symptom severity within the clinical and non-clinical groups are likely to lead to significant revisions of current findings pertaining to the effect of autism and psychosis spectrum disorders on domains that are impacted by both conditions.

Implications for the relationship between autism and psychosis

In the introduction, Figure 1.1 presented four models that propose putative relationships between autism and psychosis/schizophrenia spectrum disorders. The first is the subsume model, which posits that autism is subsumed in psychosis or vice versa. The second is the separate (or independent model), which posits that autism and psychosis are two mutually exclusive conditions. The third is the overlapping model, which suggests that both conditions feature overlapping phenotypes and exhibit shared areas of deficits. Finally, the fourth is the

diametric model, which posits that autism and psychosis are etiologically and phenotypically diametrical conditions that exert opposite effects on outcome and behavior. As pointed out in the introduction, the first model can be ruled out, as it principally predicts that individuals diagnosed with one condition would necessarily meet the diagnostic criteria of the other condition. Thus, which of the remaining three models is supported by data presented in this thesis?

By simultaneously assessing the relative expression of autism and psychosis, I was able to statistically test which of the separate, overlapping and diametric models best reflected the putative relationship between autism and psychosis (see Appendix 2). Using this approach, we uncovered that autism and psychosis have an interactive effect on performance in both the attentional and socio-cognitive domains and which also appear to be reflected at the brain level within specific subdivisions of the rTPJ. This significant interactive effect suggests that autism and psychosis expressions are unlikely to have independent effects on saliency or perspective-taking abilities, thus providing reasonable ground to rule out the independence of autism and psychosis, at least with respect to their effects on these domains. In addition, the unpacking of the interactive effect also suggested that the effects of autism and psychosis are not unidirectional or additive as would be predicted by the overlapping model—the effect engendered by one condition was moderated by the relative expression of the other, and some times even in the opposite direction. Therefore, our data do not support the overlapping model, and in fact suggest that the relationship between autism and psychosis is best described within the context of the diametric model (Crespi & Badcock, 2008).

However, the analyses of the data suggest that the diametric model as depicted by Crespi and Badcok (2008) (see Figure 1.1D) requires modifications in at least two respects in order to account for the full range of effects of autism and psychosis. First, the diametric model does not allow for the co-occurrence of autism and psychosis, as the expression of one

condition ought to be at the expense of the other. This means that comorbidity is counter to what would be predicted by the diametric model, and that any co-occurrence is likely to be a misdiagnosis of the schizophrenia premorbid condition as autism (Crespi & Crofts, 2012). While misdiagnosis is certainly a possibility (Van Schalkwyk, Peluso, Qayyum, McPartland, & Volkmar, 2015), this explanation is also likely driven by the inability of the diametric model to explain findings suggesting that the same genetic risk factor can confer risk for both autism and psychosis. For example, the risk for autism and/or schozphrenia may be associated with the same CNV loci such as 1q21.1 duplication and 16p13.1 duplication (Crespi & Crofts, 2012). In a clear departure from the diametric model, in this thesis I have simultaneously assessed both autism and psychosis within the same individual. The analyses clearly suggest that both conditions can be expressed at varying degrees, and importantly that these expressions can have measurable effects on outcome and behavior that are consistent with observations reported in the literature for each of these conditions alone. In this respect, it is important to highlight that the term comorbidity is not restricted to the categorical presence of two conditions, but also to the co-occurrence of conditions at various degrees of expression.

Second, unlike the diametric model, a population can be divided along the autism and psychosis axes into at least four groups: Two biased groups and two balanced groups (see Figure 7.1). The biased groups represent the canonical diametric axis of autism and psychosis. However, as pointed above, at each point along this axis, autism and psychosis expressions coexist at varying degrees, with the extreme points representing the clinical conditions as depicted in the original diametric model (Figure 1.1D). The balanced axis is an added dimension that allows for varying magnitudes of equal expressions of both autism and psychosis. I argue that the balanced axis is an important and necessary refinement of the original diametric model, which only allows for a single point of balance along the autism-

psychosis axis. In fact, according to the diametric model, normality corresponds to a single point of balanced mechanistic and mentalistic cognitions along its mechanistic-mentalistic continuum. Thus, the inclusion of a balanced axis that allows for varying magnitudes of equal autism (mechanistic) and psychosis (mentalistic) expressions is important as it allows us to explain the presence of factors that equally confer risk for both autism and psychosis. Taken together, the bias and the balance axes give rise to the idea that autism can be a protective factor against psychosis or its phenotypic correlates. Indeed, we have shown, for example, that saliency cost decreased with increasing expression of autism traits. This leads to the intriguing hypothesis that the resilience of individuals at high risk for psychosis can be predicted by the relative expression of autism and psychosis. It also advances the radical idea that individuals with comorbid conditions would present with better profiles than individuals with either frank autism or frank psychosis, at least in some domains.

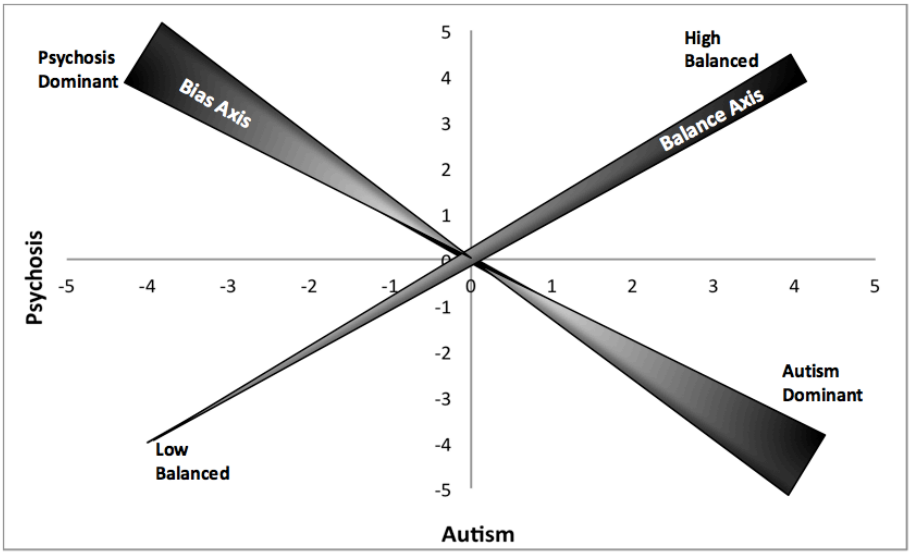

Figure 7.1. A schematic representation of the distribution of a population along the autism and psychosis axes. The balance axis represents low to high balanced expressions of autism and psychosis. The bias axis represents the relative and progressive dominance of autism or psychosis. The center is the population mean for the expression of autism and psychosis.

It is important, however, to note that similar to the diametric model, my version of the

model would also predict low occurrence of autism-psychosis comorbidity. Specifically, based on the assumption of opponency between autism and psychosis, the co-occurrence should be significantly less than the 1% prevalence rate expected for either autism or psychosis within the general population. However, a recent review of studies assessing autism and psychosis comorbidity report that the mean rate of individuals with autism-psychosis comorbidity is about 13% (Chisholm et al., 2015). However, the reported rates of comorbidity in the reviewed studies varied widely (from 0% to ~60%). Also, none of these studies were epidemiological and the figures were drawn from small sample sizes (N ranges from 16 to 217 patients). However, in the largest study to date (that was not included in the above review), comorbidity was assessed in 2123 8-year-olds with an autism diagnosis from multiple populations across the United States. The study revealed that while 10% had a comorbid psychiatric diagnosis, only about 0.4% met the diagnostic criteria for psychosis spectrum disorders. However, as psychosis spectrum disorders typically emerge during late adolescence, early adulthood, this incident rate is likely to be higher, but it would need to increase by at least 300% to be at par with the expected rate of 1% for autism or psychosis spectrum disorders within the general population. There is an obvious and an urgent need for substantial epidemiological studies to establish true prevalence of autism and psychosis comorbidity (Tsai, 2014). Data from these studies will be crucial in informing theories concerned with the nature of the relationship between these two pervasive conditions.

Clinical implications

The thesis investigated the association between autism and psychosis within healthy adults. However, based on the notion that (1) these conditions are not confined to the disorder and can be expressed to varying degrees within the clinical and non-clinical populations, and (2) that the effects observed reflect what has largely been found within the clinical entities, I

discuss, with due caution, some potential clinical implications. First and foremost, the apparent interactive nature of autism and psychosis calls for their simultaneous assessment within the individual. As such, this finding supports changes in the DSM-5, which no longer, at least in principle, considers autism and psychosis as mutually exclusive conditions. This is particularly important for tailoring individualized treatment plans. In this regard, individualized treatment plans can benefit from more studies that directly compare autism and psychosis particularly on shared phenotypes such as perspective-taking and saliency. I have shown, for example, that autism and psychosis dominant individuals appear diametric in their ability to suppress or filter out salient distractor. This finding might be used to develop *reciprocal treatments*, and provides important insights to realize the context in which condition-specific profiles can be beneficial for the individual. Accordingly, we would expect individuals with autism to perform well in tasks or contexts that require suppression of salient elements and, conversely, we would expect individuals with psychosis to perform well in contexts in which attending to salient elements bears benefits.

Second, the concept of reciprocal treatments may also be applicable for pharmacological research and intervention. If autism and psychosis can be traced to opposite biological risk factors, one might suggest that a risk for one condition can in fact be a remedy for the other. The potential of this suggestion is supported by evidence showing that psychostimulants such as amphetamine and its derivatives—known to induce psychosis—can improve specific target symptoms in autism such as hyperactivity, impulsivity, disinhibition and inattention (Nickels et al., 2008). Conversely, in utero exposure to valproic acid has been associated with increased risk for autism (Roullet, Lai, & Foster, 2013). Independently, it has been shown, albeit when given in conjunction with other medications, that valproic acid further reduces symptom severity in patients with schizophrenia (Citrome, 2002; Yoshimura, Shinkai, Ueda, & Nakamura, 2007). In addition, if autism and psychosis are predisposed by a

reciprocal biological mechanism, the development of medications with opposite pharmacokinetics can be a promising model for pharmacological treatment in autism and schizophrenia (Crespi & Go, 2015). For example, agonists of nicotinic acetylcholine receptors, which are important for sensory gating and attention, are a promising new treatment agents for schizophrenia (Freedman, 2014) and their antagonists for autism (Lippiello, 2006).

Third and lastly, much of the murkiness pertaining to the association between autism and psychosis can be attributed to the disconnect between adult and child psychiatrists—typically child psychiatrists are not trained in assessing psychosis and adult psychiatrist are not trained to assess autism. A crosstalk between these two disciplines is paramount to advancing treatments of patients with autism and psychosis.

THE INTENTIONAL STANCE

In a departure from the main theme of the present thesis, Chapter 5 addressed a fundamental drawback in research investigating the neural underpinnings of Dennett's (1987) notion of an intentional stance, and more specifically the neural underpinning of mentalizing in interactive contexts. Previous studies of intentional stance have confounded whether the opponent is a human or computer and whether the opponent is a free intentional agent or a passive agent that merely follows predetermined set of instructions. An important finding of the current study is that while adopting an intentional stance activates the "mentalizing network", it is not specific to mentalizing about humans. Specifically, believing that the opponent is an intentional agent (irrespective of the opponent being a human or a computer) activated canonical regions with the mentalizing network. These included the bilateral TPJ, the precuneus, the anterior paracingulate cortex and the right temporal pole. A subset of this network that included the right TPJ and the anterior paracingulate cortex was active when

playing human rather than a computer, which reflects spontaneous reasoning in the presence of a human agent.

In addition to the contribution of current study to research investigating the intentional stance in the context of human-computer interactions, the study demonstrated that the RPS task can be an attractive alternative to existing tasks that have been used to investigate the neural underpinning of mentalizing in clinical populations (Joyce, Averbeck, Frith, & Shergill, 2013). Studies of social cognition and its neural patterns in clinical settings have been challenged with tasks that are cognitively demanding and unengaging. The RPS task, on the other hand, can be an alternative to language- and cognitively-laden tasks such as the functional localizer task, because it is engaging, interactive, cognitively undemanding and, as demonstrated, results in a comprehensive activation of the mentalizing network. More specifically, the findings of this study should encourage the use of this task to investigate neural activation within the mentalizing network of individuals with autism and psychosis particularly in light of the evidence presented in Chapter 6, showing that autism and psychosis modulate the BOLD signal of the right TPJ generated during this task.

LIMITATIONS AND FUTURE RESEARCH DIRECTIONS

The findings and inferences presented in this thesis should be interpreted in the context of several limitations. First, the assessment of autism and psychosis relied on only two questionnaires, the AQ and the CAPE. While it would have been desirable to include additional questionnaires, these questionnaires are robust and have been standardized across many language and cultures confirming their validity. However, future studies should consider assessing the expression of these conditions using different questionnaires such as the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991) and The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) (Mason & Claridge, 2006) for the

assessment of psychosis proneness, and the Social Responsiveness Scale-Adult (SRS-A) (Constantino & Todd, 2005) for the assessment of autism tendencies.

Second, the tasks used in the study are limited in their ability to offer a mechanistic account of how autism and psychosis interact to achieve their effect. For example, the perspective-taking paradigm cannot distinguish between the types of errors produced by autism-dominant individuals and those produced by psychosis-dominant individuals. Therefore, there is a need to develop paradigms that can distinguish between errors that are due to under-mentalizing (as would be predicted for autism) versus errors of hyper-mentalizing (as would be predicted for psychosis). Such methodological advances would be a critical next step to understanding how autism and psychosis interact to improve perspective-taking and information processing.

Third, the small sample size of the imaging study limited our ability to conduct a whole-brain analysis as a function of autism, psychosis and their interaction. Therefore, I opted for a region of interest-based approach, which suggested that the activity within the rTPJ during a mentalizing task is interactively modulated by autism and psychosis expressions. Larger studies are required to examine the extent to which this effect can be observed in the brain, particularly within interacting systems such as the ventral and dorsal attentional systems or the default mode network (DMN) and the positive task network (PTN). This research is important in that it can offer a neurobiological mechanism for the interactive effect of autism and psychosis on functional outcomes.

Fourth, some may question the stability of the interaction between autism and psychosis, as symptoms in clinical psychosis are transient and in autism are not. While it is true that psychosis symptoms can be ameliorated, the rate of recovery for the majority of patients is rather low (Insel, 2010). In addition, improved symptoms in these patients are often not accompanied with improved functional outcomes or with the reversal/restoration of

causal mechanisms (Insel, 2010). Thus the biological mechanisms underlying the diametric effect are likely to be trait markers, which is consistent with the view of schizophrenia as a neurodevelopmental condition.

Fifth, some may question the generalizability of the current findings as it is based on university samples. Pleasingly, however, the obtained scores for both the AQ and the CAPE scores were consistent with the distribution of scores reported for these questionnaires within the general population. One might even suspect that the observed effects in the current studies are likely to be larger once examined within the general population. Relatedly, the samples in the studies reported in this thesis largely consisted of female participants. While gender had no effect on our findings, in a sample with equal sex ratios, the observed effects are likely to be stronger due to the expected greater expression of autism traits of male participants in the population (Baron-Cohen et al., 2014).

The findings in this thesis are expected to stimulate further research not to only for the purpose of replicating the current findings, but to also address some of the limitations raised in this section. It would be intriguing for future research to search for contexts where the interaction between autism and psychosis does not result in a benefit or that the effects are specific to one condition or the other. The experiments conducted in this thesis examined the interactive effect of autism and psychosis within the attentional and socio-cognitive domains. Will, for example, the same effect be observed within the affective domain? In this regard, both autism- (Magnuson & Constantino, 2011) and psychosis-specific (Siris, 2000) symptoms are associated with elevated levels of depression and difficulties with affect regulation, and so one might predict that their interaction would lead to increased levels of depression, rather than an improvement. Similarly, is this interactive effect generalizable, for example, to general intelligence and early stages of information processes, or is it only present at higher cognitive processes? These and similar questions are important to test the

veracity and specificity of the hypotheses generated by the findings presented in this thesis, namely the diametric effect of autism and psychosis on outcome measures.

Equally important is to test the extent to which autism traits interact with other dimensions of schizotypy/psychosis. For reason outlined in this thesis, I only tested the interactive effect of autism traits and the expression of positive psychotic symptoms. In the case of the CAPE, it consists of three factors representing positive, negative and depressive symptoms. Examining the degree and manner in which the depressive and negative symptoms interact with the expression of autism traits is important to determining the uniqueness of the interactive effect between autism traits the expression of positive symptoms. However, these factors and particularly the negative symptoms tend to correlate highly with the expression of autism traits. Disentangling autism traits from negative symptoms is paramount to understanding the degree to which autism and psychosis spectrum disorders are related, which currently is unfortunately complicated by the underspecificity of available instruments for the assessment of autism traits and negative symptoms.

In addition, a major challenge for research is the development of appropriate analytic tools that can capture the effect of co-occurring pathologies on an outcome measure. The mean and bias effect model presented in Chapter 2 and 4 offers a novel analytic approach for this problem, and thus it may be an important complement to standard analytic approaches. Importantly, I have shown that interactions in linear models naturally resolve into quadratic terms that assume either a sub-additive relationship between the two conditions (i.e., a bias effect) or an additive relationship between the two conditions (i.e., a mean effect). This suggests that the use of linear correlations may mask the complexity of the effect of independent variables on the dependent variable. It is important to note in this context that linear analytic approaches are only a first approximation of the effect of independent variables on the dependent variable, but not necessarily the best summary of the effects.

Moreover, while the bias and mean effect model is more complex and less parsimonious than the standard linear regression model, it is in fact its mathematical equivalent, but with the advantage of uncovering both linear and non-linear effects. Thus, the utilization of an analytic approach that combines both linear and nonlinear effects can have measurable benefits to understanding the effect of comorbid conditions on outcome and behaviour (or any two variables on an outcome), in that it can statistically support or refute putative assumptions about the relationship of comorbid conditions (or variables), and how this relationship affects the dependent variable. With regard to autism and psychosis, I have shown that their concurrent effect on perspective taking and saliency cost is generally captured by the quadratic term of the bias effect. The bias effect suggests that the effect of one condition is dependent on the relative, rather than the absolute expression of the condition, possibly reflecting the compensatory relationship of systems that are preferentially expressed in autism and psychosis. Importantly, the quadratic term of the bias effect also suggests that autism and psychosis have diametric effects on intentional and socio-cognitive phenotypes, which is most apparent by the identical performance of participants with high tendencies to both disorders to participants presenting with low tendencies to both disorders (see for example Figure 2.3 and Figure 4.8).

CONCLUSION

The thesis converges on many fields, including attention, social cognition, cognitive neuroscience and psychiatry, making it a project with broad impacts. The findings and the methodological approaches reported in this thesis can be used to develop specific and informed hypothesis about the relationship between autism and psychosis within the clinical and non-clinical populations. They also inform our understanding of inter-individual differences in core abilities important for social communication and functioning. More

significantly, the findings should encourage the assessment of both autism and psychosis traits in both the clinical as well as the control groups, which could have important consequences for establishing baseline measures. If confirmed, the impact of the current findings can be large enough to change the way the field examines autism and psychosis and their effect on behavioural and brain phenotypes.

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APPENDIX 1

Table 1. Mean (± SD) of AQ and CAPEp scores, Proportions of Perspective-Taking Errors and Reaction Times of correct responses in the experimental and control conditions for the ambiguous and relational trials.

	Participants (N=201)	Perspective-Taking Error (Proportions)	Reaction Times of Correct Responses[§]
AQ	16.33±6.30		
CAPEp	27.37±4.84		
Ctrl_Ambig		0.01±0.03	2542 (225)
Exp_Ambig		0.05±0.08	2568 (294)
Ctrl_Relat		0.21±0.16	3005 (306)
Exp_Relat[†]		0.42±0.35	2991 (421)

*AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences. Ctrl = Control; Ambig= Ambiguous; Exp= Experimental; Relat= Relational.

[§] A comparison between the RTs of the ambiguous and relational trials is not possible due to the inherent difference in the time of onset of the critical referent in the ambiguous and relational instructions—time of referent onset in the ambiguous trials is about 724ms after the start of the instruction, and 1047ms in the relational trials (for complete details see Apperly et al., 2010).

[†] Data is based on 187 participants due to 14 participants erring (or erring and timing out) on all experimental relational trials. Participants timed out on 3.6% of all possible 1608 trials.

As can be seen from Supplementary Table 1, there were no differences between RT times of the control and experimental trials in both the ambiguous (t(200)=-1.63; p=.11) and relational conditions (t(186)=.93; p=.35). This pattern is consistent with that observed by Apperly et al. (2010). Moreover, Pearson correlations reveal that the participants' correct responses on the experimental trials were unrelated to reaction times (*ps*>.50).

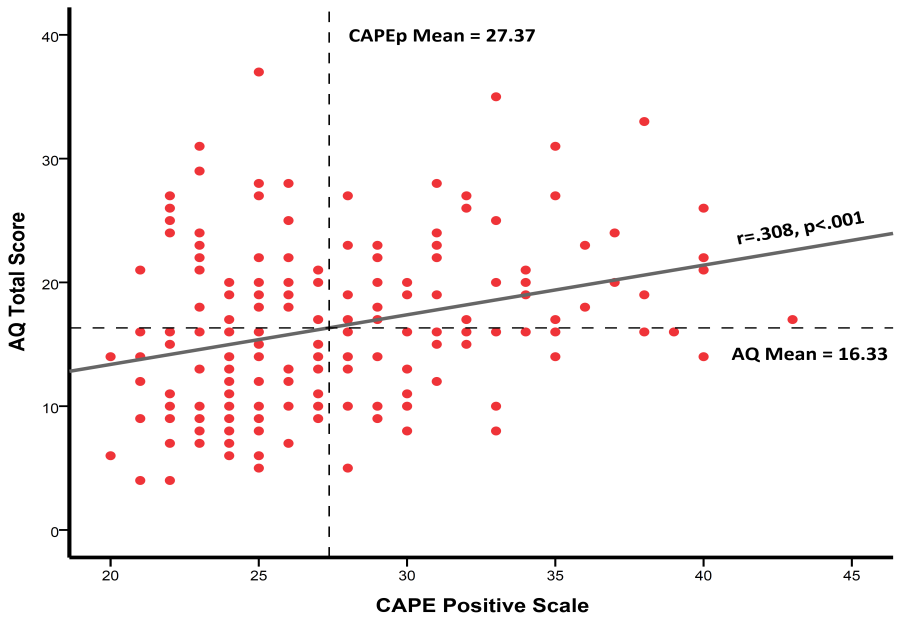

Figure 1. A scatter plot depicting the association between the Autism Spectrum Quotient Scale (AQ) scores and the scores on the Positive scale of the Community Assessment of Psychic Experiences (CAPE positive scale, CAPEp).

Table 2. Summary of Poisson regression coefficients with errors on the experimental **relational** trials as the dependent variable and gender as a covariate

Model* / Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	-1.61	.4348	13.709	1	.200	<.001
AQ	.054	.0230	5.483	1	1.055	**=.019**
CAPEp	.044	.0152	8.293	1	1.045	**=.004**
Gender	-.087	.0537	2.647	1	.916	=.104
AQxCAPEp	-.002	.0008	4.969	1	.998	**=.026**

AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences.
***** Omnibus test (χ^2 =15.89 df=4, p=.003)

Table 3. Summary of Poisson regression coefficients with errors on the experimental **ambiguous** trials as the dependent variable

Model* / Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	-1.494	.9810	2.321	1	.224	=.128
AQ	.086	.0537	2.572	1	1.090	=.109
CAPEp	.076	.0368	4.268	1	1.079	**=.039**
AQxCAPEp	-.003	.0020	2.786	1	.997	**=.095**

AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences.
***** Omnibus test (χ^2 =5.108 df=3, p=.164)

Table 4. Summary of Poisson regression coefficients of the bias model with errors on the experimental **relational** trials as the dependent variable and gender as a covariate

Model* / Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	-.391	.1059	13.636	1	.676	<.000
Bias (AQz-CAPEpz)	-.019	.0240	.619	1	.981	=.431
Bias^2	.020	.0096	4.375	1	1.020	**=.036**
Sum (AQz+CAPEpz)	.034	.0196	2.943	1	1.034	=.086
Sum^2	-.010	.0088	1.207	1	.990	=.272
Bias x Sum	-.005	.0126	.130	1	.995	=.718
Gender	-.079	.0556	2.002	1	.924	=.157

AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences.
***** Omnibus test (χ^2 =16.39, df=6, p=.012)

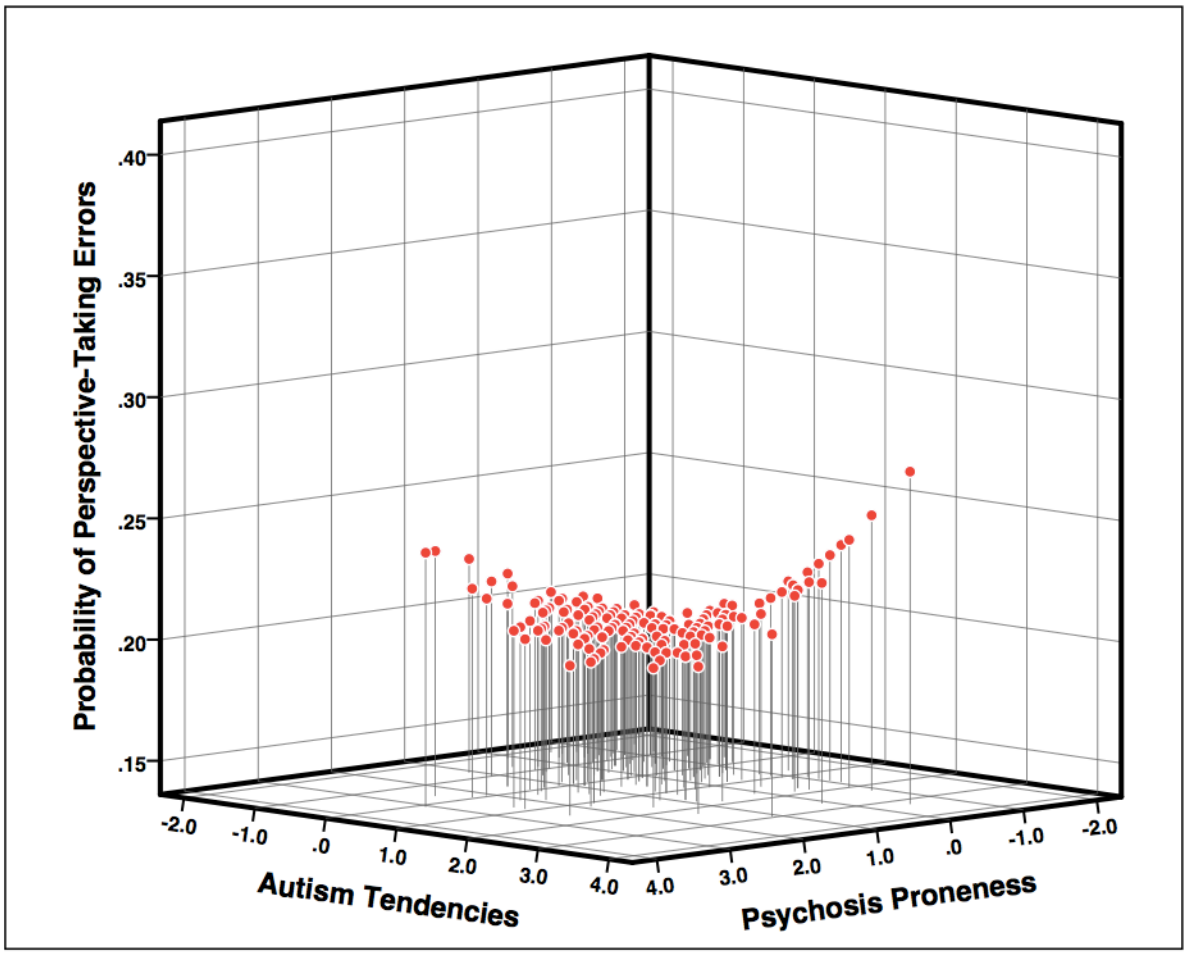

Figure 2: 3-D representation of the relationship between autism tendencies and psychosis proneness (represented as standardized Z scores) and the probability of making perspective-taking errors on the ambiguous trials. The negative scores represent low tendencies and the positive scores represent high tendencies. (Omnibus test (χ^2 =4.14, df=5, p=.53)).

Reference:

Apperly, I. A., Carroll, D. J., Samson, D., Humphreys, G. W., Qureshi, A., & Moffitt, G. (2010). Why are there limits on theory of mind use? Evidence from adults' ability to follow instructions from an ignorant speaker. *Q J Exp Psychol (Hove), 63*(6), 1201-1217. doi: 10.1080/17470210903281582

APPENDIX 2

Reconceptualizing the effect of co-occurring autism and psychosis traits on cognition and behavior in terms of bias and mean effects: A mathematical rationale

Diagnostic and non-diagnostic features of autism and psychosis can co-occur in the same individual. The concurrent effect of Autism (A) and Psychosis (P) on cognition and behavior, can be captured in a model with just three dependent terms (i.e. linear terms plus interaction) as follows:

(1) **Y = i*A + j*P + k*A*P +ε, where i, j and k are best fit parameters [Model 1]**

However, the relationship between these conditions can alternatively be expressed in terms of Bias (i.e., the relative dominance of one condition vis-à-vis the other—or a sub-additive effect) and mean effect (i.e., an additive effect).

If the Bias (B) and Mean effect (M) terms are defined as:

(2) B = (A - P)/2
(3) M = (A + P)/2

then autism (A) and Psychosis (P) can be expressed as:

(4) A = M + B (by adding equations (2) and (3))
(5) P = M – B (by subtracting equations (2) from (3))

By substituting A and P in Model 1 with their values from equations (4) and (5), the initial model is in effect identical to the following:

(1) **Y = i*A + j*P + k*A*P +ε, where i, j and k are best fit parameters [Model 1]**

(6) y = i*(M+B) + j*(M-B) + k*(M+B)*(M-B) →

(i+j)*M + (i-j)*B + k*(M^2) - k*(B^2),

or **m*M + n*B + o*M^2 + p*B^2 +ε**, where m, n, o and p are best fit parameters.

If we are setting up such a model from scratch we would naturally want to include the interaction term between M and B, resulting in a model with 5 dependent variables as follows:

(7) Y = m*M + n*B + o*M^2 + p*B^2 + q*M*B +ε [Model 2]

This is therefore the initial preferred model for M and B. Note that the implication from above is that the interaction term between A and P (in Model 1) resolves into a simple multiple of (M^2-B^2). The question then becomes for Model 1 above whether most of the variance in the **A*P** interaction term is carried by the M^2 or the B^2 portion (or whether it is shared equally). If the answer to this question is that the B^2 (or the M^2) term alone carries a disproportionate amount of the variance then this is a strong reason for arguing that using the derived Bias/Mean-effect formalism is inherently more useful and meaningful than using the base A and P scores used in Model 1. Conversely, if the result is that the variance is shared equally (between M^2 and B^2) then that would seem to argue that there is no advantage in the conversion, and that descriptions in terms of A and P are adequate (and more interpretable).

APPENDIX 3

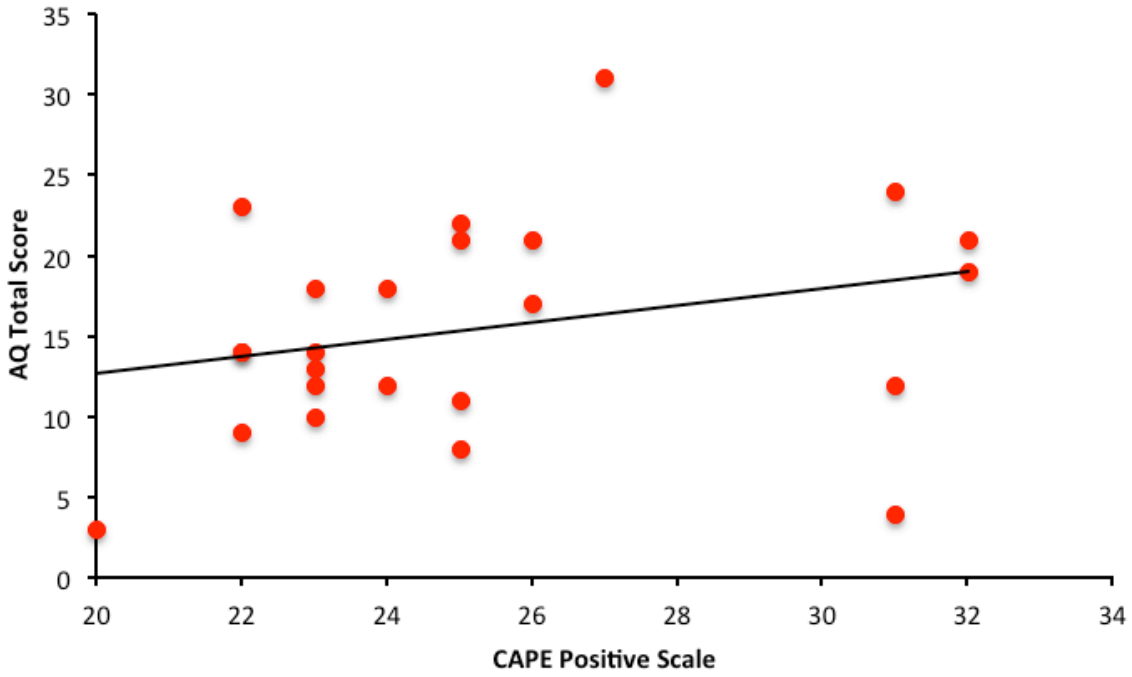

Figure 1. A scatter plot depicting the association between the Autism Spectrum Quotient Scale (AQ) scores and the scores on the Positive scale of the Community Assessment of Psychic Experiences (CAPE positive scale, CAPEp).

Table 1. Summary of coefficients with mean percent signal change of the rTPJ (=rvpTPJ) as the dependent variable.

Model / Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	.219	.064	11.81	1	1.25	**=.001**
AP	.096	.083	1.34	1	1.10	=.25
HC	-.091	.088	1.06	1	.91	=.30
APxHC	.039	.118	.11	1	1.04	=.74
AQ	-.070	.028	6.54	1	.93	**=.011**
CAPEp	.102	.027	13.74	1	1.11	**<.001**
AQxCAPEp	.077	.022	11.86	1	1.08	**=.001**

AP= Active-Passive; HC= Human-Computer; AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences.

Table 2. Summary of coefficients with mean percent signal change of the rvaTPJ as the dependent variable.

Model Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	.040	.047	.72	1	1.04	=.40
AP	.041	.068	.37	1	1.04	=.54
HC	-.035	.063	.31	1	.97	=.58
APxHC	.034	.094	.13	1	1.035	=.71
AQ	-.013	.020	.38	1	.99	=.54
CAPEp	-.052	.018	8.20	1	.95	**=.004**
AQxCAPEp	.073	.015	24.53	1	1.08	**<.001**

AP= Active-Passive; HC= Human-Computer; AQ= Autism Quotient; CAPEp= Positive scale of the Community Assessment of Psychic Experiences.

Table 3. Summary of coefficients with mean percent signal change of the rvaTPJ as the dependent variable with the attention-switching subscale of the AQ as a covariate, controlling for CAPEp scores.

Model* Coefficient	β	(SE)	Waldχ^2	df	Exp(β)	Sig.
Constant	.059	.04	1.63	1	1.06	=.20
AP	.041	.067	.38	1	1.04	=.54
HC	-.035	.064	.29	1	.97	=.59
APxHC	.034	.094	.13	1	1.04	=.72
Attention-Switching	**.069**	**.025**	**7.77**	**1**	**1.07**	**=.005**

* Coefficients are estimates of a Generalized linear model (χ^2 =15.30, df=5, p=.009, R^2=.13), where the Active vs. Passive (AP) and Human vs. Computer (HC) were entered as fixed factors, and the participants' standardized Z scores of the attention-switching subscale of the AQ as a covariate. Higher scores on the attention-switching subscale reflect poor attention-switching or strong focus of attention.