A comparison of the autism and schizophrenia spectrums

By

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DECLARATION

I certify that this thesis has been composed by me personally and that the work contained

herein is my own, except where clearly indicated.

I certify that this work has not been submitted for any other degree or professional

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I hereby grant the University of Edinburgh the right to publish this thesis and abstract,

and to authorise its publication for any scholarly purpose with proper acknowledgement

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<u>Dr Andrew C. Stanfield</u>

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ABSTRACT

Although they share a number of clinical features, autism and schizophrenia are usually distinguished by their different ages of onset and certain discriminating features such as major impairments to communication in the former and positive psychotic symptoms in the latter. However, the recognition that these conditions are part of broader spectrums of impairment has led to the definition of disorders which do not show such marked and discriminating features, such as autism spectrum disorders (ASD) and schizotypal personality disorder (SPD). Reviewing the historical development of these concepts and areas of potential overlap or difference between them revealed that they have both shared and discriminating features, but no study to date has directly compared them. Three experiments were therefore conducted to compare ASD and SPD using clinical, neuropsychological and functional magnetic resonance imaging (fMRI) techniques.

In the clinical experiment, standardised measures were used to determine if it was possible to distinguish between the groups, and to allow their quantitative comparison. It was possible to distinguish between ASD and SPD in most cases, although 17% of the population tested met criteria for both conditions. This 'comorbid' (CM) group were therefore considered separately. When a single diagnosis could be allocated, there were clear overlaps of clinical features between the conditions and each condition showed more traits of the other than were seen in controls. The overlaps were most prominent for negative schizotypal traits which did not differ between the groups. The CM group were more affected than either the ASD or SPD groups across multiple domains. All groups had high levels of previously undiagnosed psychopathology.

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In the neuropsychological experiment, tests of social cognition, executive function and central coherence / local-global processing bias were employed. The similarities between the ASD and SPD groups were striking. Both showed similar evidence of impairment in social cognition and executive function, although there was some evidence of greater impairment in working memory in the ASD group. Differences were seen using a test of local-global processing bias, although these were potentially confounded by differences in general intellectual ability.

Two fMRI tasks were conducted: a working memory task (a letter based n-back task) and a social judgment task (where individuals made judgements of either gender or approachability from a picture of a face). The former did not distinguish between the ASD and SPD groups. In the latter, individuals with SPD showed significantly greater activation than the ASD group in several brain regions known to be associated with social cognition, with the controls scoring in-between the two.

Although they show marked clinical and brain functional overlaps, the results of the fMRI task of social judgement suggest that it is correct to consider ASD and SPD as separate diagnostic entities. The findings are consistent with the idea that, although both conditions are associated with impairments in understanding the mental states of others (mentalising), the mechanism which underlies these differs between the groups, with ASD associated with hypo-mentalising and SPD associated with hyper-mentalising.

STRUCTURE OF THESIS

The following thesis concerns the relationship between the broader spectrum forms of autism and schizophrenia, commonly referred to as autism spectrum disorders (ASD) and schizotypal personality disorder (SPD). It is divided into two introductory chapters, three experimental chapters and a conclusion.

Chapter 1 contains a historical perspective on the development of the current concepts of ASD and SPD.

Chapter 2 reviews the existing literature with regard to the potential shared and discriminating features of ASD and SPD.

Chapter 3 contains the first experiment of the thesis: a comparative study of the clinical features displayed by groups of people with ASD and / or SPD.

Chapter 4 is the second experiment of the thesis: a comparison of the neuropsychological characteristics displayed by the same groups.

Chapter 5 is the third experimental section: a comparison of the same groups using functional magnetic resonance imaging.

Chapter 6 contains the conclusion to the study.

Chapter 1

Conceptual development and classification of schizophrenia spectrum and autism

spectrum disorders

1.1: INTRODUCTION

Psychiatry is unusual in modern medicine as being the only speciality where almost all of the conditions treated are classified on the basis of their observed symptoms and signs, as opposed to the biologically oriented classificatory systems which characterise other branches of medical practice. Perhaps unsurprisingly, diagnostic certainty and consistency are difficult to achieve with such a state of affairs, a problem most clearly illustrated by the USA-UK prevalence studies of schizophrenia in the 1970s (Wing 1971).

The relationship between autism and schizophrenia is one area of psychiatry in which the difficulties of clinically based classificatory systems quickly become apparent. As will be expanded later in this chapter, the term autism was originally developed for a symptom of schizophrenia; it became a diagnosis in its own right in the 1940s but was quickly encompassed in the following years by an ever broadening concept of schizophrenia; in the 1970s autism was reclassified as an independent disorder, which it has essentially remained until the modern day when questions about the relationship between autism and schizophrenia have started to re-emerge (Crespi and Badcock 2008; Nylander, Lugnegård et al. 2008; Carroll and Owen 2009; Craddock and Owen 2010), with some even proposing the reverse of the historical position, i.e. that schizophrenia is a form of autism (King and Lord 2011).

This relationship becomes particularly confusing when one considers that there are putative subtypes of each condition where the more easily identifiable distinguishing

features are less prominent, making their distinction more difficult.   Of course, classificatory systems do exist for these 'spectrum' disorders - schizophrenia related personality disorders and autism spectrum disorders (such as Asperger syndrome) are not infrequent diagnoses in modern psychiatry.   In general these diagnostic categories are regarded as being mutually exclusive (American Psychiatric Association 2000). However, whether these spectrum disorders are truly independent of each other is unclear (Wolff 1995) and there is little research available to guide either the practitioner or the academic working in this field.

The initial step in determining the relationship between the autism and schizophrenia spectrums is to consider the historical background against which these diagnostic categories arose and how they have developed since the original descriptions of their more marked forms.   In doing so, it may be possible to discern differences in the evolution of these diagnoses which may enlighten the nature of their relationship.

1.2: SCHIZOPHRENIA SPECTRUM DISORDERS

1.2.1: A brief history of schizophrenia

Schizophrenia, as currently defined, has resulted from the amalgamation of a number of different conceptualisations of the condition.   Although commonly taught that the development of these concepts occurred as a linear progression until such time as the true (current) definition of the disorder became apparent, it has been argued that the condition

actually represents the (con)fusion of ideologically distinct concepts (Berrios, Rogelio et al. 2003). Regardless of which of these perspectives is taken it remains true that the most influential of these on our modern day ideas of the disorder are Emil Kraepelin's dementia praecox (Kraepelin 1899) and Kurt Schneider's "symptoms of the first rank" (Schneider 1959) but the name by which the condition is known remains that coined by Eugen Bleuler in 1908 (Bleuler 1987).

Kraepelin

Emil Kraepelin first used the term dementia praecox in the 4th edition of his textbook *Psychiatrie - ein Lehrbuch für Studierende und Ärzte* (Psychiatry - a Textbook for Students and Physicians) (Kraepelin 1893) . Here he includes it under the section heading of *Die Psychischen Entartungsprocesse* (the Degenerative Psychoses) and equates it with the concept of *hepehrenie*, previously described by Ewald Hecker (Hecker 1871). In this section he also includes the condition *katatonie*, based upon Karl Kahlbaum's *katatonie* (Kahlbaum 1874) and his own *dementia paranoides* (which was in turn based upon Kahlbaum's *paranoia* (Kahlbaum 1863), all as separate disorders. In the 5th edition of his textbook (Kraepelin 1896), this classification persists under the heading *Verblödungsprocesse* (Processes of Mental Deterioration) and it is not until the 6th edition in 1899 that he subsumes *hebephrenie*, *katatonie* and *dementia paranoides* under the heading dementia praecox (Kraepelin 1899). The characteristic feature of dementia praecox, according to Kraepelin, was the "development of a peculiar kind of psychological enfeeblement" and he used this to separate these conditions from manic-depressive insanity on the basis of their inevitably deteriorating course. In addition to the

rapid development of "psychological enfeeblement", Kraepelin also emphasised the importance of delusions, hallucinations, impaired attention, thought incoherence, stereotyped movements and expressions, deterioration of emotional life and a loss of drive as key symptoms of the condition – features which are still accorded importance today in modern descriptions of the condition (see Figure 1.1).

It is worth noting that, Kraepelin was guided by the principle that dementia praecox was a condition which was entirely biological in nature and which, when enough was known about it, would eventually be shown to have a clear biological cause. However, although suggesting that *hebephrenie*, *katatonie* and *dementia paranoides* ought to be classified together, Kraepelin also recognised the clinical value in maintaining the different subtypes of dementia praecox:

"From a clinical standpoint it is perhaps better for the sake of clarity to keep the three main groups of dementia praecox apart, but they are undoubtedly connected" (Kraepelin 1899)

Bleuler

The first recorded use of the term schizophrenia occurred in a monograph by Eugen Bleuler in 1908 (Bleuler 1987). Bleuler felt that dementia praecox was a misnomer and that his new term, schizophrenia, highlighted the key feature of the disorder – a splitting of the psychic functions:

"I would like to emphasize that Kraepelin's dementia praecox is not necessarily either a form of dementia or a disorder of early onset. For this reason, and because there is no adjective or noun which can be derived from the term dementia praecox, I am taking the liberty of using the word schizophrenia to denote Kraepelin's concept. I believe that the tearing apart or splitting of psychic functions is a prominent symptom of the whole group." (Bleuler 1987)

From the above it is clear that, similar to Kraepelin, Bleuler did not view schizophrenia as single disease entity; indeed his seminal text on the subject was called "*Dementia Praecox oder Gruppe der Schizophrenien*" – "Dementia Praecox or the Group of Schizophrenias." (Bleuler 1950)

Although he stated that the group of schizophrenias and dementia praecox were the same conditions, Bleuler placed much less emphasis than Kraepelin on what we would now see as positive psychotic symptoms. Although Bleuler was convinced of the physical nature of schizophrenia, his attempts to understand the symptomatology of the disorder were influenced by psychodynamic concepts prevalent in the early 20th century. Indeed, in the foreword to his 1911 textbook he specifically states that his ideas represent an '*application of Freud's ideas to dementia praecox*' (Bleuler 1950) although others have cited the theories of Pierre Janet and his work on dissociation as having greater influence on Bleuler (Moskowitz and Heim 2011).

Against this background Bleuler developed the idea that *"the splitting of the different psychic functions is one of its* [schizophrenia's] *most important features."* Splitting of the mental functions was a metaphor commonly used in the 19th century as an explanation for unusual behaviour in a wide variety of contexts (Berrios, Rogelio et al. 2003). Although he awarded it the status of being the most important part of the schizophrenic state, the exact nature of Bleuler's concept of splitting is not clear (Berrios, Rogelio et al. 2003; Moskowitz and Heim 2011). There appear to be two main contexts in which Bleuler used the term: firstly to denote what his son, Manfred Bleuler, has described as "the dissociation of thoughts, of emotions, of attitudes and of acting" (Bleuler and Bleuler 1986); secondly to relate to the inconsistent domination of the schizophrenic personality by different ideologically charged affective states (complexes) which become split from each other leading to disintegration of the personality (Stotz-Ingenlath 2000; Berrios, Rogelio et al. 2003; Moskowitz and Heim 2011).

In addition to splitting, Bleuler also developed the idea that the features of schizophrenia could be divided into categories using two categorical axes: fundamental-accessory (i.e. characteristic of schizophrenia / also present in other disorders) and primary-secondary (i.e. core to the disorder / arising from other features). The fundamental features of schizophrenia were: loosening of associations, disturbances of affectivity, ambivalence, and autism. Of these only loosening of associations was also a primary feature which could explain the others (Bleuler's concept of loosening of associations was broader than the current use as a form of thought disorder (Moskowitz and Heim 2011)); delusions, hallucinations and catatonic symptoms were both accessory and secondary phenomena.

As will be detailed later, Bleuler therefore introduced the term autism as a description of a feature of schizophrenia; he defined it as "*detachment from reality, together with the relative and absolute predominance of the inner life*" (Bleuler 1950).

Although modern authors have emphasised the differences between Kraepelin's and Bleuler's formulations of schizophrenia (Berrios, Rogelio et al. 2003; Kuhn 2004; Moskowitz and Heim 2011), their writings do often appear to be describing the same group of conditions. However, Kraepelin, in the main, restricted himself to the observable clinical features with the apparent belief that these related to an underlying biological dysfunction; Bleuler's descriptions went beyond this as he attempted to describe the psychological mechanisms by which he believed many of the obvious clinical features of the disorder were generated out of the primary biological deficit(s). This approach is consistent with the psychodynamic influences on Bleuler's work (and indeed bears comparison to the modern field of cognitive neuroscience). One would think that Bleuler's approach would result in a more narrow delineation of the disorder involving as it does a fusion of clinical observations and mechanistic propositions. However, his assertions that the fundamental features could be present without the accessory phenomena ('simple schizophrenia' and 'latent schizophrenia (see section 1.1.2)), and that often the only signs of schizophrenia are symptoms that are not necessarily pathological (e.g. "*Character anomalies, indifference, lack of energy, unsociability, stubbornness, moodiness, the characteristic for which Goethe could only find the English word whimsical, hypochondriacal complainists etc.*") (Bleuler 1950) led

to Bleuler's schizophrenia becoming a much wider category than Kraepelin's original ideas of dementia praecox (Hoenig 1983).

Schneider

Like Bleuler and Kraepelin, Schneider regarded schizophrenia as a biological disorder. However, unlike them, he aimed to define the symptoms of psychosis in a way that did not depend upon causal or mechanistic theories, instead relying solely upon clinical observation. Originally writing in 1939, Schneider defined his so-called "*symptoms of the first rank*" which he asserted were always indicative of schizophrenia in the absence of an organic cause:

"audible thoughts, voices heard arguing, voices heard commenting on one's actions; the experience of influences playing on the body (somatic passivity experiences); thought withdrawal and other interferences with thoughts; diffusion of thought, delusional perception, and all feelings, impulses (drives) and volitional acts that are experienced by the patient as the work or influence of others." (Mellor 1970)

The presence of first rank symptoms was considered by Schneider to be sufficient to diagnose schizophrenia. However, they were not necessary for the diagnosis to be made; a combination of second rank symptoms (those which could also be found in other conditions) and behavioural abnormalities would suffice. Second rank symptoms of schizophrenia included: other disorders of perception, sudden delusional ideas,

perplexity, depressive and euphoric mood changes and feelings of emotional impoverishment (Schneider 1959).

The modern concept of schizophrenia

Schneider's work gained particular traction in British psychiatry where it was used as the basis for the Present State Examination (Wing, Birley et al. 1967). However in the USA Bleuler's work held sway for many years, in particular the idea that schizophrenia could be diagnosed by the presence of the fundamental features alone. This divergence of clinical practice meant that individuals presenting with the same clinical picture would be more likely to receive a diagnosis of schizophrenia in the USA than the UK, a fact which also influenced the conceptual development of the broader schizophrenia spectrum (see Section 1.2.2). The emergence of the neo-Kraeplinian movement in the 1960s led to a re-alignment of British and American concepts of schizophrenia with a de-emphasis of the fundamental features and greater importance being placed upon positive psychotic symptoms. The current DSM-IV diagnostic criteria used to define schizophrenia are shown in Figure 1.1.

A. *Characteristic symptoms:* Two (or more) for the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):

1. delusions
2. hallucinations
3. disorganised speech (for example frequent derailment or incoherence)
4. grossly disorganised or catatonic behaviour
5. negative symptoms, that is, affective flattening, alogia, or avolition

> **Note:** Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. *Social/occupational dysfunction:* For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. *Duration:* Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (that is, active-phase symptoms) and may include prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (for example, odd beliefs, unusual perceptual experiences).

D. *Schizoaffective and Mood Disorder exclusion:* Schizoaffective Disorder and Mood Disorder With Psychotic Features have been ruled out because either (1) no Major Depressive, Manic, or Mixed Episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. *Substance/general medical condition exclusion:* The disturbance is not due to the direct physiological effects of a substance (for example, a drug of abuse, a medication) or a general medical condition.

F. *Relationship to a Pervasive Developmental Disorder:* If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are present for at least a month (or less if successfully treated).

Figure 1.1: DSM IV-TR diagnostic criteria for schizophrenia

1.2.2: Conceptual development of schizophrenia spectrum disorders

Modern ideas of the schizophrenia spectrum have been heavily influenced by the re-analysis of the Copenhagen sample of the Danish Adoption Studies (Kety, Rosenthal et al. 1975) led by Robert Spitzer as part of the development process for DSM-III (Spitzer, Endicott et al. 1979). However, the histories that were re-examined by Spitzer et al were mainly cases which were in themselves diagnosed in the original studies as either borderline schizophrenia or uncertain borderline schizophrenia. In his seminal review of the history of schizotypal personality disorder, Kendler asserts that the criteria used for borderline schizophrenia in the Danish Adoption Studies and the derivation of DSM-III diagnostic criteria were based upon two major traditions - descriptions of atypical personality traits in relatives of people with schizophrenia and clinical reports of people who displayed symptoms of schizophrenia but without marked delusions, hallucinations or personality deterioration (Kendler 1985).

Familial Tradition

The beginnings of the familial approach are seen shortly after Kraepelin's first delineation of dementia praecox. In the 8th edition of his textbook (originally published in German in 1909 and presented for an English audience in 1919) he notes:

"*Not infrequently one learns further that among the brothers and sisters of the patients there are found striking personalities, criminals, queer individuals, prostitutes, suicides, vagrants, wrecked and ruined human beings, all being forms in which more or less well-developed dementia praecox may appear*" (Kraepelin 1919)

As demonstrated by his belief in the importance of his fundamental features of schizophrenia, Bleuler too was aware of the broader spectrum of schizophrenia, where these features could be in evidence but without accessory symptoms such as delusions and hallucinations. Bleuler used the term simple schizophrenia for those individuals who showed only the fundamental features of the condition and implied that it was familially related to the more severe forms of the condition:

"*Thus, there is no doubt that many simple schizophrenics are at large whose symptoms are not sufficiently pronounced to permit the recognition of mental disorder. If one observes the relatives of our patients, one often finds in them peculiarities which are qualitatively identical with those of the patients themselves, so that the disease appears to be only a quantitative increase of the anomalies seen in the parents and siblings*" (Bleuler 1950)

Although he describes several cases of simple schizophrenia Bleuler does not actually define the condition in any specific way. Some element of deterioration in function is present in all the cases he describes but he also comments that "*there are many simple schizophrenics among eccentric people of every sort who stand out as world saviours and world reformers, philosophers, writers and artists, beside the 'degenerated' and deteriorated.*"

In the same section of his monograph as simple schizophrenia Bleuler proposes the concept of '*latent schizophrenia.*' Unfortunately he felt that was '*not necessary to give a detailed description of…latent schizophrenia*' but does provide the below:

"*There is also a latent schizophrenia, and I am convinced that this is the most frequent form, although admittedly these people hardly ever come for treatment…..In this form we can see in nuce all the symptoms and all the combinations of symptoms which are present in the manifest types of the disease. Irritable, odd, moody, withdrawn or exaggeratedly punctual people….Often one discovers a concealed catatonic or paranoid symptom and exacerbations occurring in later life demonstrate that every form of this disease may take a latent course.*" (Bleuler 1950)

Despite these and other (see (Kendler 1985)) isolated and rather imprecise descriptions of unusual personality traits in relatives of people with schizophrenia the first detailed exploration of these phenomena appears in part II of "*Physique and Character*" by Ernst Kretschmer (Kretschmer 1925). Kretschmer is probably most famous now for his description of the asthenic, pyknic and athletic body types, but a large portion of his work was devoted to the consideration of temperament and personality, in particular those associated with major mental disorder.

Kretschmer defined two types of normal personality – schizothymic and cyclothymic – which when present to a pathological degree he labelled as schizoid and cycloid respectively. These were regarded as the temperamental counterparts to schizophrenia

and bipolar disorder (or circular insanity as it was then sometimes called), which he judged as '*nothing other than marked accentuations of normal types of temperament.*' He was concerned not just with the 'p*re-psychotic personality of the sick individual himself*' but also asserted that '*the typical characteristics of the constitutional type may sometimes be more clearly delineated in the nearest relations than in the patient himself*' (Kretschmer 1925) (Figure 1.2).

TABLE X.

TYPE OF SCHIZOPHRENE FAMILY.

Father's Sister.	Father.	Mother.	Mother's Sister.	Mother's Brother.
Unsociable and extraordinarily excitable.	Paranoiac eccentric, anxiety, misanthropic, depressed.	Short persecution-mania with alcoholism in pre-senile period, sensitive, humourless, pedantic, depressed. Pressure at a distance.	Avaricious.	Alcoholism. Vagrant.

1. *Brother*	2. *Patient.*	3. *Brother.*	4. *Brother.*
Inventor, stormy puberty, depressed, passionate, restless. Pressure at a distance.	Schizophrenia. Persecution-mania with acute katatonic attacks. Quiet, eccentric, conscientious, depressed, with chronic feeling of inferiority and a strong capacity for phantasy.	Shy with other people, conscientious, good at his business. (Like 2.)	Quiet, serious, logically minded, unsociable. Pressure at a distance.

Figure 1.2: Family tree of a schizophrenic individual, taken from Kretschmer (1925)

He outlines three main types of schizoid personality,

1. Unsociable, quiet, reserved, serious (humourless), eccentric.

2. Timid, shy, with fine feelings, sensitive, nervous, excitable, fond of nature and books.

3. Pliable, kindly, honest, indifferent, dull-witted, silent.

and emphasises that the core aspect of the schizoid personality is type 1 or what he earlier in the book equates to Bleuler's autism, by which he means 'living inside oneself' or giving no sign on the surface of true ideas or feelings. It appears that Kretschmer felt that this was, at least in part, an unconscious process:

 '*One cannot know how they feel; sometimes they don't know themselves*'

Kretschmer outlines hyperaesthetic ('*emotionally sensitive, abnormally tender, constantly wounded, mimosa-like natures who are all nerves*') and anaesthetic ('*insensitive and cold*', ' *lack of affective resonance*') components to the schizoid personality which are usually present in varying amounts in a single individual's '*psychaesthetic proportion*'. Both components lead to different forms of autism, either through a protective response to an unpleasant hypersensitivity to the environment and others (found in hyperaesthetics), or through a lack of emotional response to the world (found in anaesthetics):

'*He draws himself back into himself, because he has no reason to do anything else, because all that is about him can offer him nothing.*" (Kretschmer 1925)

In addition to the core social dysfunction Kretschmer also mentions other traits, not discussed by Kendler, including a tendency towards mystical religiosity, an overformal way of speaking and particularity about the appearance. Interestingly, in the context of future definitions of autism, he also suggests that people with a schizoid personality have

a preference for "*office work that goes on mechanically, according to fixed rules and regulations*" and that this results from an affected person's desire to protect themselves from the effects of their hyperaesthesia; similarly, that shutting oneself away leads, in some, to a "*building up of their own world out of thoughts and favourite pursuits.*"

The first systematic exploration of the schizophrenia spectrum in families of people with schizophrenia was conducted by Franz Kallmann and published in his 1938 book "The genetics of schizophrenia" (Kallmann 1938). He identified 1,087 patients with schizophrenia admitted to the Herzberge Hospital of Berlin in the first ten years of its opening and studied 13,851 of their relatives (12,153 genetically related) using a number of different sources of information. Around 10% of these relatives were found to have schizophrenia; however 25% met criteria for the broader category "*schizoidia.*" Within schizoidia Kallmann defined two categories: borderline cases and schizoid psychopaths. Borderline cases were described as "*eccentric personalities….masked schizophrenics, postpsychotic cases after short attacks, and all the various schizoid personalities with peculiar and emotionally defective attributes.*" He considered borderline cases as "*latent schizophrenics and not as carriers of a schizoid constitution*" and that "*they form, in the scale of the schizophrenic disease complex, the transition from homozygotic trait-carriers with definite schizophrenic processes to the schizoid psychopaths.*" Schizoid psychopaths were defined as "*individuals who showed the fundamental schizoid characteristics of autistic introversion, emotional inadequacy, sudden surges of temperament and inappropriate motor response to emotional stimuli*" and included "*stubborn and perverse recalcitrants, malicious and cold-hearted despots, superstitious*

and pietistic religio-maniacs, secretive recluses, sectarian dreamers out of touch with reality, and the over-pedantic, avaricious and literal-minded people" (Kallmann 1938).

Following Kallmann and prior to the Danish Adoption Studies, there were several family studies which gave detailed descriptions of atypical personality traits found in relatives of people with schizophrenia. Slater lists five traits which he identified as associated with having a relative diagnosed with schizophrenia: paranoid traits, eccentricities, lack of feeling, reserve (incapacity for warmth) and anergia (Slater 1953). Stephens described increased rates of three personality types in relatives of people with schizophrenia: psychopathic, paranoid and schizoid. These were defined as follows:

"The term psychopathic personality was applied to persons whose lives were characterized by lack of restraint, antisocial, aggressive or criminal trends, emotional instability, or irresponsibility. Paranoid personality, described those who were consistently hostile, not only to the interviewer but also to acquaintances, neighbours and hospital staff but expressed no overt delusions. Two rather distinct subgroups were included under the term schizoid personality: (i) individuals who were socially withdrawn from choice, shy, submissive, lacking initiative, or unable to establish emotionally warm or close relationships; (ii) individuals who were rambling, vague, unrealistic and often excessively anxious at interview and appeared to be eccentric and solitary in their personal lives." (Stephens, Atkinson et al. 1975)

Thus, within the familial tradition the key traits which separated family members of people with schizophrenia from the general population are eccentricity, irritability, social

isolation, affective coldness and suspiciousness (Kendler 1985). Although some authors refer to superstitiousness, mysticism and mild positive symptoms these are not given a primary role in distinguishing relatives of people with schizophrenia from unaffected individuals.

Clinical Tradition

The clinical tradition, as defined by Kendler, is composed of case reports of individuals who presented with traits which the treating clinician felt to be fundamentally related to schizophrenia, but which fell short of the full diagnosis. It is worth noting that these clinicians were primarily dynamic psychotherapists practicing in the USA at a time when the diagnosis of schizophrenia was more broadly applied in North America than it was in Europe (Wing 1971). Although each of the authors reviewed by Kendler specifically linked the condition they described to schizophrenia, their reasoning for doing so must be viewed within the psychodynamic construct and broad definition of schizophrenia prevalent at that time in the USA.

Zilboorg described "*ambulatory schizophrenias*" in 1941 and illustrated his ideas using three cases – all men convicted of murder (Zilboorg 1941). The term crops up commonly in the psychiatric literature in the following few decades and is often likened to Bleuler's latent schizophrenia (Hollender 1959). Zilboorg himself coined the term because the condition was such that although the men had a form of schizophrenia they appeared superficially typical and could therefore be treated as outpatients; in response to its increasingly widespread application he later stressed that it is the superficial typicality

rather than the outpatient nature of their treatment that defines the condition (Zilboorg 1957). In such cases, Zilboorg felt that "*autistic contemplation, or, as Bleuler preferred to term it later, dereistic thinking*" was "*the outstanding feature of any schizophrenia*". This thinking could be manifest as anything from a taciturn nature to active social withdrawal accompanied by purposeless wandering between jobs or interests, and an increased preoccupation with bodily symptoms to the point that many presented with somatic complaints. Patients were said to show illogical thinking and give vague rambling answers to questions but marked thought disorder, delusions or hallucinations were absent (Hollender 1959).

Helene Deutsch, who studied for a short time with Kraepelin, but later became a firm adherent of Freud, described the "*as-if*" personality which she felt may represent a prodromal phase of schizophrenia. The term "*as-if*" was adopted by her as she felt that "*every attempt to understand the way of feeling or manner of life of this type forces on the observer the inescapable impression that the individual's whole relationship with life has something about it which is lacking in genuineness and yet outwardly runs along 'as if' it were complete*" (Deutsch 1986). Affected individuals were said to have a poor sense of sense of self-identity and have no connection with their emotional state but lacked awareness of these deficits. Despite these difficulties they tended to display little sign of disorder other than the sense of inauthenticity as they could compensate by mimicking others in "*a spasmodic, if skilled, repetition of a prototype without the slightest trace of originality*."

In 1949 Hoch and Polatin described a condition which they termed '*pseudoneurotic schizophrenia*' and presented 5 case studies as examples (Hoch and Polatin 1949). The term pseudoneurotic was chosen as such cases often presented initially as neuroses but later it would become evident that they were in fact forms of schizophrenia. Hoch and Polatin take the Bleulerian view that schizophrenia is defined by the presence of fundamental symptoms and describe how these are present in more subtle forms in pseudoneurotic schizophrenia. From a symptomatic perspective, these individuals commonly presented with extreme anxiety and 'pan-neurosis', a state which differed from that seen in typical neurotic patients due to its all-encompassing nature, pervading many aspects of the patients life and including multiple different neurotic symptoms. Individuals were said to be unable to describe or give explanations of their anxiety, not moving beyond vague, repetitive and stereotyped descriptions of their symptomatology. Magical thinking was commonly elicited in relation to phobic symptoms. Brief psychotic episodes, termed by the authors as 'micropsychosis' were also relatively common and thought to evolve in a gradual fashion. During these episodes, hypochondriacal ideas, ideas of reference and depersonalisation were particularly significant symptoms and patients showed a tendency to "zig-zag repeatedly over the reality line". Atypical psychosexual organisation or 'polymorphous perverse manifestations' were held to be an important feature of the condition. None of the patients described had a family history of schizophrenia. Later Hoch formalised the diagnostic criteria as in Figure 1.3 (Hoch and Cattell 1959) and presented outcome data showing that 20% of affected people went on to develop schizophrenia with half of those showing chronic forms of the disorder (Hoch, Cattell et al. 1962).

Table 1. The Diagnosis of Pseudoneurotic Schizophrenia

The Primary Clinical Symptoms:
  1. Disorders of Thinking and Associations: Process; Content.
  2. Disorders of Emotional Regulation: Form; Content.
  3. Disorders of Sensorimotor and Autonomic Functioning.
The Secondary Clinical Symptoms:
  1. Pan-Anxiety.
  2. Pan-Neurosis: Neurotic Symptomatology, Acting-Out Behavior and Character-Disorder Symptoms.
  3. Pansexuality.

Figure 1.3: Diagnostic criteria for pseudoneurotic schizophrenia, from Hoch and Cattell (1959)

In 1953 Sandor Rado coined the term schizotype, during a lecture given to the American Psychiatric Association (Rado 1953). Although, the lecture was an exposition of psychodynamic classification, Rado used the term schizotype as a condensation of schizophrenic phenotype. Rado viewed the schizotype as the inherited disposition towards developing schizophrenia and that a number of psychodynamic traits, together called the schizotypal organisation, were detectable in genetically vulnerable individuals regardless of whether they ever suffered a frank psychotic illness. The primary aspect of the schizotypal organisation was held to be an "*integrative pleasure deficiency*", leading to a lack of the "*motivational strength*" of the "*machinery of psychodynamic integration.*" As a result, schizotypal individuals are required to (unconsciously) adopt several compensatory mechanisms to prevent disintegration; these are the conservation of their limited resource of pleasure, marked dependence on others and the substitution of rational intellectual thought for emotional pleasure.

The work of Paul Meehl in 1962 represents one of the first attempts to produce an integrative model of psychosis via the concept of schizotypy (Meehl 1962). Meehl proposed that the inherited deficit in schizophrenia was one of neural integration, which he labelled schizotaxia, and that this was most likely due to aberrant synaptic control. All schizotaxic individuals were then postulated to develop a personality structure which, following Rado, Meehl called schizotypal. The degree of schizotypal traits and whether an individual developed clinical schizophrenia was dependent upon environmental influences acting upon the individual. The primary schizotypal feature was held to be "*cognitive slippage*" – essentially a mild form of thought disorder. Other features which may or may not be present depending upon the environment and social learning experienced by an individual were: interpersonal aversiveness ("*social fear, distrust, expectation of rejection, and conviction of his own unlovability*"); anhedonia ("*a marked, widespread, and refractory defect in pleasure capacity*"); and ambivalence. Meehl also commented that autistic and dereistic thinking were secondary to the other features – "*Crudely put, if a person cannot think straight, gets little pleasure, and is afraid of everyone, he will of course learn to be autistic and dereistic.*"

Thus, within the clinical tradition, as described by Kendler (1985), the key components of the schizophrenia spectrum were considered to be magical or fantastical thinking, mild thought disorder evidenced by an idiosyncratic communication style, attenuated psychotic symptoms, anhedonia and a lack of interpersonal relations.

DSM-II concepts of the schizophrenia spectrum

Although there were many different names for schizophrenia spectrum disorders in use at the time, DSM-II largely took its lead from Bleuler's nomenclature through the inclusion of three relevant disorders – simple schizophrenia, latent schizophrenia and schizoid personality (American Psychiatric Association 1952). Paranoid personality disorder was also included in DSM-II but it should be noted that, although there are clear symptomatic overlaps with paranoid schizophrenia, paranoid personality disorder has historically been considered as more similar to delusional disorders or paraphrenia than to schizophrenia (Akhtar 1990).

The characteristic symptoms of schizophrenia in DSM-II were felt to be alterations of concept formation (which may lead to psychologically self-protective delusions and hallucinations); ambivalent, constricted and inappropriate emotional responsiveness and loss of empathy; and regressive bizarre behaviour. Simple schizophrenia was used for cases with a slow and insidious onset of withdrawal, apathy and indifference leading to progressive functional deterioration, but without marked positive psychotic symptoms. Latent schizophrenia was applied to individuals who clearly presented with the characteristic features of schizophrenia but who had no history of positive psychotic symptoms. Pseudo-neurotic and borderline schizophrenia were included here. Schizoid personality disorder was characterized by shyness, over-sensitivity, seclusiveness, avoidance of close or competitive relationships, and often eccentricity. Autistic thinking, daydreaming and an inability to express hostility and aggression were held to be common

and affected people were thought to react to disturbing events with detachment, however they did not lose the capacity to recognize reality.

Danish Adoption Study of Schizophrenia

The Danish Adoption Register contains the details of all legal, non-familial adoptions in Denmark between 1924 and 1947 – 14,425 in total. The register was established in the early 1960s with the primary purpose being to examine the genetic and environmental influences on the development of schizophrenia (Petersen and Sorensen 2011). The initial study focused on the smaller Copenhagen sample of 5483 (Petersen and Sorensen 2011). The prevalence of schizophrenia in biological relatives of adopted people with schizophrenia was 5.6% and the prevalence of the "borderline state" was 14.8% (Kety, Rosenthal et al. 1968). The borderline state was specified as including "pseudoneurotic schizophrenia, border-line, ambulatory schizophrenia, questionable simple schizophrenia, "psychotic character" [and] severe schizoid individual". The characteristics of the borderline state were:

"i) Thinking: strange or atypical mentation: thought shows tendency to ignore

reality, logic and experience (to an excessive degree) resulting in poor adaptation to life

experience (despite the presence of a normal IQ); fuzzy, murky, vague speech.

ii) Experience: brief episodes of cognitive distortion (the patient can, and does, snap back but during the episode the idea has more the character of a delusion than an ego-alien obsessive thought); feelings of depersonalization, of strangeness or unfamiliarity with or toward the familiar: micropsychosis.

iii) Affective: anhedonia - never experiences intense pleasure - never happy; no deep or intense involvement with anyone or anybody.

iv) Interpersonal behaviour: may appear poised, but lacking in depth ("as if" personality); sexual adjustment: chaotic fluctuation, mixture of heterosexuality and homosexuality.

v) Psychopathology: multiple neurotic manifestations which shift frequently (obsessive concerns, phobias, conversion, psychosomatic symptoms, etc.): severe widespread anxiety."

(Kety, Rosenthal et al. 1968)

As Kendler points out, many of these criteria were derived from amalgamations of concepts taken from the clinical tradition with Hoch's pseudoneurotic schizophrenia given particular prominence; in contrast, the majority of features from the familial tradition are not mentioned (Kendler 1985).

DSM-III to the present day

The development of DSM-III represented a dramatic shift in the classification of disorders which were considered to be possibly related to schizophrenia, with the removal of some long-established diagnostic categories, the reformulation of others and the development of new disorders (American Psychiatric Association 1980). Most strikingly, a new condition called schizotypal personality disorder was created which included many individuals previously classified under simple schizophrenia, latent schizophrenia or schizoid personality disorder (Figure 1.4). The term schizoid

personality disorder was retained but with a much more limited scope and the classification of paranoid personality disorder remained unchanged. This classificatory system has remained broadly unchanged since then, despite draft proposals for DSM-5 making the case for significant alterations (see below).

DSM II   **DSM III**

| Simple Schizophrenia | ┄┄┄┄┄➤ | Schizotypal Personality Disorder |

| Latent Schizophrenia | ┄┄┄┄┄➤ | Schizotypal Personality Disorder |
| | | Borderline Personality Disorder |

Schizoid Personality	┄┄┄┄┄➤	Schizotypal Personality Disorder
		Schizoid Personality Disorder
		Avoidant Personality Disorder

| Paranoid Personality | ┄┄┄┄┄➤ | Paranoid Personality Disorder |
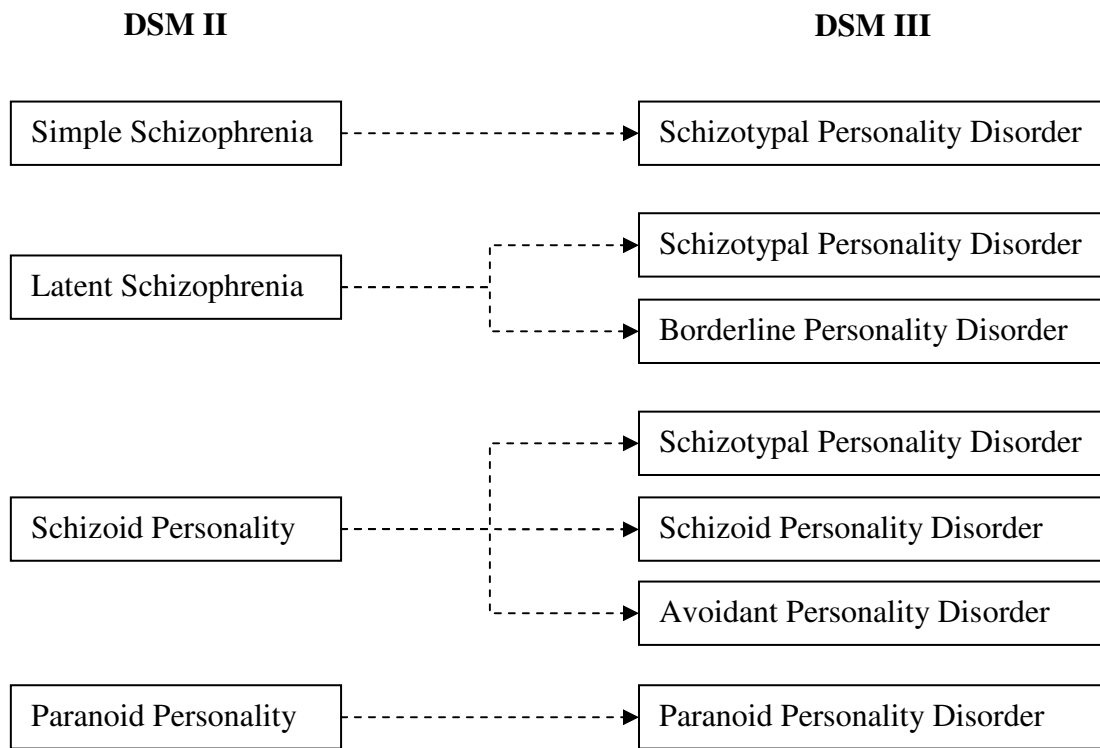
Figure 1.4: Changes in schizophrenia spectrum related diagnostic categories between DSM-II and DSM-III

The criteria for schizotypal personality disorder were derived from a reanalysis of data from the Danish Adoption Study by Robert Spitzer, who was leading the development of DSM-III, and colleagues (Spitzer, Endicott et al. 1979). Spitzer and colleagues began by consulting with the authors of the Danish Adoption Study to develop a 24 item list of the characteristics they had used to diagnose borderline states. They then applied this list to 36 cases from the Danish Adoption Study with diagnoses of borderline states. These

cases included both individuals with relatives who had schizophrenia and others who were relatives of controls. However, they found that many clinical features of these cases were not captured by the 24 items and that many of the items were not seen in any of the cases. They therefore re-examined the cases, noting important clinical features and collapsed these into 17 items. When re-applied to the cases they found that using eight of the items allowed them to separate borderline states from non-schizophrenia spectrum individuals with a sensitivity of 86% and a specificity of 95%. These eight items were somewhat validated through a large survey of clinicians working with individuals diagnosed with borderline states and were chosen to form the basis of schizotypal personality disorder in DSM-III, although not without controversy at the time (Spitzer, Endicott et al. 1979). Since then they have been largely validated through detailed studies of relatives of people with schizophrenia (Kendler and Gruenberg 1984; Kendler, McGuire et al. 1993; Kendler, Gruenberg et al. 1994; Maier, Lichtermann et al. 1994; Chang, Chen et al. 2002; Tienari, Wynne et al. 2003). Possibly as a result, the diagnostic category of schizotypal personality disorder, has remained largely unchanged since its adoption, with the only alteration for DSM-IV being the addition of a ninth item covering eccentricity (American Psychiatric Association 2000) (Figure 1.5).

A. A pervasive pattern of social and interpersonal deficits marked by acute discomfort with, and reduced capacity for, close relationships as well as by cognitive or perceptual distortions and eccentricities of behaviour, beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

1. ideas of reference (excluding delusions of reference)
2. odd beliefs or magical thinking that influences behaviour and is inconsistent with subcultural norms
3. unusual perceptual experiences, including bodily illusions
4. odd thinking and speech (eg. vague, circumstantial, metaphorical, overelaborate or stereotyped)
5. suspiciousness or paranoid ideation
6. inappropriate or constricted affect
7. behaviour or appearance that is odd, eccentric, or peculiar
8. lack of close friends or confidants other than first-degree relatives
9. excessive social anxiety that does not diminish with familiarity and tends to be associated with paranoid fears rather than negative judgments about self

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder and is not due to the direct physiological effects of a general medical condition

Figure 1.5: DSM-IV diagnostic criteria for schizotypal personality disorder

Much of the focus during the development of DSM-III personality disorders was upon the clarification of the two major usages of the term 'borderline' at that time (borderline schizophrenia, or borderline states as it was called in the Danish American Adoption Study, and borderline personality disorder). This work allowing for the categorisation and creation of operationalised criteria for schizotypal personality disorder and borderline personality disorder (Spitzer, Endicott et al. 1979). However, other decisions potentially relevant to the study of the schizophrenia spectrum included the diminishment of the previously broadly defined category of schizoid personality disorder and the retention of paranoid personality disorder. Compared to the derivation of schizotypal personality disorder, there is little information in the literature regarding the rationale for and validation of these decisions. Similarly, there are substantial changes to both schizoid and paranoid personality disorder between DSM-III and DSM-IV with little available rationale. For paranoid personality disorder, more emphasis is placed on mistrust in

DSM-IV (See Figure 1.6) whereas DSM-III also contained sections regarding hypersensitivity and restricted affectivity. Compared to DSM-III, DSM IV schizoid personality disorder contains additional items related to the deliberate avoidance of others (items 1-4 in Figure 1.7).

A. A pervasive mistrust and suspiciousness of others such that their motives are interpreted as malevolent, beginning in early adulthood and present in a variety of contexts, as indicated by four (or more of the following:

    1. suspects, without sufficient basis, that others are exploiting, harming or deceiving him or her
    2. is preoccupied with unjustified doubts about the loyalty of associates
    3. is reluctant to confide in others because of unwarranted fear that the information will be used maliciously against him or her
    4. reads hidden, demeaning or threatening meanings into benign remarks/events
    5. persistently bears grudges, i.e. is unforgiving of insults, injuries or slights
    6. perceives attacks on his or her character or reputation that are not apparent to others and is quick to react angrily or to counterattack
    7. has recurrent suspicions, without justification, regarding fidelity of spouse or partner

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, or another psychotic disorder and is not due to the direct physiological effects of a general medical condition

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Figure 1.6: DSM-IV diagnostic criteria for paranoid personality disorder

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A. A pervasive pattern of detachment from social relationships and a restricted range of expression of emotions in interpersonal settings, beginning by early adulthood and present in a variety of contexts, as indicated by four (or more) of the following:

    1. neither desires nor enjoys close relationships, including being part of a family
    2. almost always chooses solitary activities
    3. has little, if any, interest in having sexual experiences with another person
    4. takes pleasure in few, if any, activities
    5. lacks close friends or confidants other than first degree relatives
    6. appears indifferent to the praise or criticism of others
    7. emotional coldness, detachment or flattened affectivity

B. Does not occur exclusively during the course of schizophrenia, a mood disorder with psychotic features, another psychotic disorder, or a pervasive developmental disorder and is not due to the direct physiological effects of a general medical condition
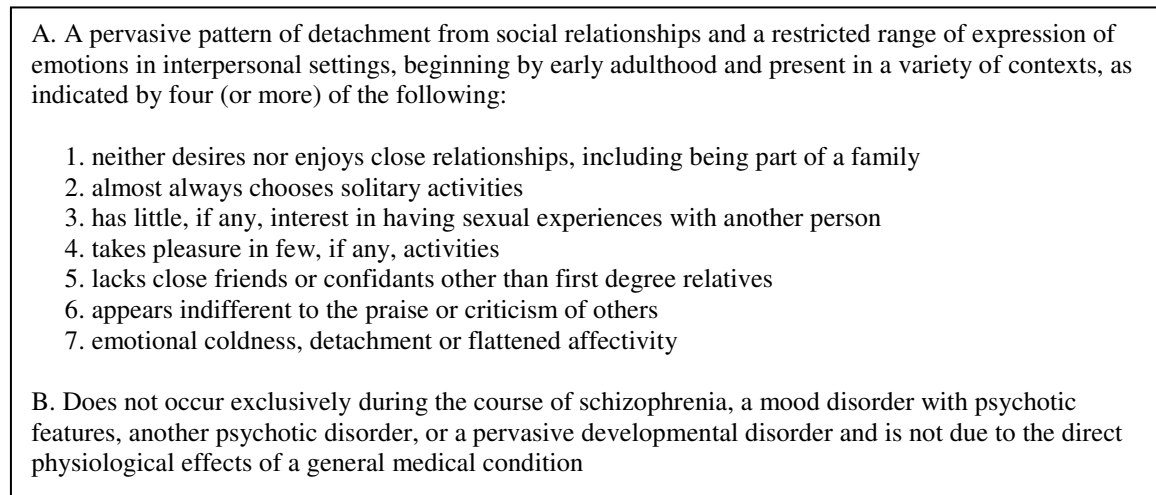

Figure 1.7: DSM-IV diagnostic criteria for schizoid personality disorder

Importantly, although paranoid, schizoid and schizotypal personality disorders are commonly seen as related to each other (e.g. all three are commonly referred to as Cluster A or the 'odd' personality disorders) and there are clear overlaps in their symptomatology, the status of schizoid personality disorder and paranoid personality disorder in relation to the schizophrenia spectrum remains unclear. As discussed above the postulated relationship between schizotypal personality disorder and schizophrenia has been clearly validated by family studies; this is not the case for schizoid and paranoid personality disorder where the literature is more conflicting (Kendler and Gruenberg 1984; Kendler, McGuire et al. 1993; Kendler, Gruenberg et al. 1994; Maier, Lichtermann et al. 1994; Chang, Chen et al. 2002; Tienari, Wynne et al. 2003).

The future of the schizophrenia spectrum

In December 2012 the latest version of the Diagnostic and Statistical Manual for Mental Health Disorders, DSM-5, was signed off by the trustees of the American Psychiatric Association. The initial draft, produced in 2010, proposed a radical shake-up of the personality disorder section, with five of the ten categories being dropped and the introduction of an additional new six item dimensional scale. Two of the five categories put forward for exclusion were schizoid personality disorder and paranoid personality disorder. However, these ideas have been rejected, being placed instead in the 'require more research' section and the original ten categories have been maintained with no dimensional scale to be used. The exact criteria for each disorder remain unknown but a June 2011 draft of the proposed criteria for schizotypal personality disorder are shown in Figure 1.8. Although the majority of the DSM-III / DSM-IV criteria have been retained

in criterion B ('pathological personality traits') much of criterion A ('impairments in personality functioning') is new. Of particular relevance to the current study is the inclusion of an impairment in empathic function, a characteristic more classically associated with autism spectrum disorders.

The essential features of a personality disorder are impairments in personality (self and interpersonal) functioning and the presence of pathological personality traits. To diagnose schizotypal personality disorder, the following criteria must be met:

A. Significant impairments in **personality functioning** manifest by:
    1. Impairments in **self functioning**:
        a. **Identity**: Confused boundaries between self and others; distorted self-concept; emotional expression often not congruent with context or internal experience.
        b. **Self-direction**: Unrealistic or incoherent goals; no clear set of internal standards.
    2. Impairments in **interpersonal functioning**:
        a. **Empathy**: Pronounced difficulty understanding impact of own behaviors on others; frequent misinterpretations of others' motivations and behaviors.
        b. **Intimacy**: Marked impairments in developing close relationships, associated with mistrust and anxiety.

B. Pathological **personality traits** in the following domains:
    1. **Psychoticism**, characterized by:
        a. **Eccentricity**: Odd, unusual, or bizarre behavior or appearance; saying unusual or inappropriate things.
        b. **Cognitive and perceptual dysregulation**: Odd or unusual thought processes; vague, circumstantial, metaphorical, over-elaborate, or stereotyped thought or speech; odd sensations in various sensory modalities.
        c. **Unusual beliefs and experiences**: Thought content and views of reality that are viewed by others as bizarre or idiosyncratic; unusual experiences of reality.
    2. **Detachment**, characterized by:
        a. **Restricted affectivity**: Little reaction to emotionally arousing situations; constricted emotional experience and expression; indifference or coldness.
        b. **Withdrawal**: Preference for being alone to being with others; reticence in social situations; avoidance of social contacts and activity; lack of initiation of social contact.
    3. **Negative Affectivity**, characterized by:
        a. **Suspiciousness**: Expectations of – and heightened sensitivity to – signs of interpersonal ill-intent or harm; doubts about loyalty and fidelity of others; feelings of persecution.

C. The impairments in personality functioning and the individual's personality trait expression are relatively stable across time and consistent across situations.

D. The impairments in personality functioning and the individual's personality trait expression are not better understood as normative for the individual's developmental stage or socio-cultural environment.

E. The impairments in personality functioning and the individual's personality trait expression are not solely due to the direct physiological effects of a substance (e.g., a drug of abuse, medication) or a general medical condition (e.g., severe head trauma).

Figure 1.8: Proposed DSM-5 diagnostic criteria for schizotypal personality disorder

1.3: AUTISM SPECTRUM DISORDERS

1.3.1: Conceptual development of autism spectrum disorders

The introduction of autism as a term

As described in the previous section, the term autism was initially coined by Eugen Bleuler to describe what he felt was a characteristic feature of people with schizophrenia. The term itself is derived from the Greek 'autos' meaning 'self', combined with the suffix 'ismos' meaning action or state, thus it is appropriate that Bleuler used it to describe people who have "*cut themselves off as much as possible from any contact with the external world*" and who show "*detachment from reality, together with the relative and absolute predominance of the inner life*" (Bleuler 1950). Although his definition referred to patients' internal lives, Bleuler described a wide variety of observable behavioural presentations which arose out of autism: difficulty in forming relationships with others, withdrawal into the self, indifference, rigidity, inappropriateness, aberrant logic, unusual priorities, inappropriateness and a tendency towards delusional ideas (Parnas, Bovet et al. 2002). Bleuler's autism was developed in a different direction by his student and colleague, Eugene Minkowski, who regarded it as the manifest features of the core cause ('trouble génératuer') of schizophrenia – a lack of the 'vital contact with reality' (Urfer 2001). This lack of vital contact is evidenced in patients by unusual behaviours which show no regard for the usual societal demands or expectations: one example he gives is of a patient surprised at being arrested for trying to hand deliver a letter to the American ambassador protesting at the sentence of two anarchists to death; another concerns a lady who buys a majestic piano quite at odds with her apartment

(Urfer 2001); a third is of a boy who constantly questions his family seemingly without purpose other than to interrogate (Minkowski, Targowla et al. 2001). Interestingly the latter case, Paul, has several distinct qualities which one would associate with the modern day concept of the autism spectrum, although Minkowski clearly regarded him having schizophrenia.

The introduction of autism as a condition

Although there exist historical and clinical descriptions of individuals who would likely have fit modern diagnostic criteria for an autism spectrum disorder (Frith 2003) there was no clear attempt to delineate the condition as a distinct disorder until a paper by Grunya Sukhareva in 1926 entitled "*Die Schizoid Psychopathien im Kindesalter*" (Schizoid Psychopathy in Childhood) (Wolff 2004). Here she described six boys aged between 2 and 14 years old with a common constellation of symptoms which would now be subsumed under autism spectrum disorders (particularly Asperger Syndrome):

"*odd type of thinking….autistic attitude….flatness and superficiality of emotion…. sticking to tasks which had been started….psychic inflexibility with difficulty adapting to novelty….impulsive, odd behaviour…stereotypic neologisms….suggestibility…motor impairments.*"

By labelling them as having schizoid personality disorder Sukhareva acknowledged that these children displayed a clinical picture which shared certain features of schizophrenia,

but she emphasised that the condition which they presented with "*differs profoundly from schizophrenia in terms of its pathogenesis.*"

Although Sukhareva has been described as the "beloved teacher" of child psychiatrists in the Soviet Union (Rollins 1972) and this paper is now generally accepted as being one of the first attempts to delineate autism spectrum disorders as distinct diagnostic entities, this case series remained essentially unknown in the Western world until it was translated by Sula Wolff in 1996, long after others had been awarded primacy. It is interesting to reflect on the vagaries of chance, language, institution, orientation and affiliation that determine whether such descriptions become seminal papers or pass into the archives as interesting historical footnotes.

The first widely publicised use of the term autism to describe a distinct condition was in 1943 by Leo Kanner, the Director of Child Psychiatry at The Johns Hopkins Hospital in Baltimore. Kanner's seminal case series concerned 11 children with a condition he defined as an "*autistic disturbance of affective contact*" (Kanner 1943). According to Kanner, the pathognomonic characteristic of this condition was the "*inability to relate to themselves in the ordinary way to people and situations from the beginning of life*" or an "*extreme autistic aloneness.*" Three of the eleven children were mute, while the other eight showed disturbances in the use of language to communicate meaning, including pronounced delayed echolalia. Other key characteristics were "*monotonously repetitious*" behaviour, an "*anxiously obsessive desire for the maintenance of sameness*", intolerance to loud noises and moving objects, excellent rote memory and good cognitive

potential. Although Kanner recognised the similarities of the condition he described to schizophrenia ("*extreme autism, stereotypy and echolalia*"), he discriminated it on the immediately postnatal onset of his disorder, the childrens' rigid need for sameness and the gradual improvement shown by many of the children, as opposed to the progressive dementia of schizophrenia. In addition to emphasising the uniqueness of the condition, Kanner also clearly states his belief that, although the parents are mostly "*limited in genuine interest in people*", the difficulties that the children presented with were innate and could not be exclusively explained by aberrant parental relations.

Hans Asperger was a German psychiatrist who in 1944, apparently unknown to Kanner, published descriptions of 4 cases of a condition he termed "*der autistichen psychopathie*" (autistic psychopathy – psychopathy being equivalent to the modern term personality disorder) (Asperger 1991). He regarded the fundamental difficulty in these children, and the 200 others he claimed to have seen, as being a limitation of their social relationships. Perhaps the most vivid summary he gives of the social difficulties is:

"*Autistic children are egocentric in the extreme. They follow only their own wishes, interests and spontaneous impulses, without considering restrictions or prescriptions imposed from outside….They do not show deliberate acts of cheek but have a genuine defect in their understanding of another person……For personal distance too they have no sense of feeling….they unconcernedly lean on others….run their fingers over them as if they were a piece of furniture…impose themselves without shyness on anybody. They may demand a service or simply start a conversation on a theme of their own choosing.*

All this goes, of course, without any regard for differences in age, social rank or common courtesies." (Asperger 1991)

In addition, children were said to appear unfeeling towards their parents and to regularly carry out "*autistic acts of malice*" as a result of not being aware they are hurting others, either physically or mentally. Their ability to learn through social imitation was limited, instead they were forced to use "*elaborate rules and laws*" to learn.

Asperger also describes the children's unusual speech: the rhythm and tone of speech are disturbed, unusual novel expressions and neologisms are employed, and, although the children show "*highly sophisticated linguistic skills*" there was often a lack of true communicative function to their language. Non-verbal communication was also felt to be impaired; children were said to display only fleeting gaze for both people and objects and they had a paucity of facial expression and gestures.

In addition to the social and communication difficulties Asperger described the presence of stereotypic behaviour, overabsorption in preoccupations and a tendency to collect items. He also identified hypersensitivity to sensation, in both a positive and a negative fashion.

Asperger ascribes great importance to what he calls "*autistic intelligence*" which is evidenced by originality and unconventional thinking and language; interestingly this is held to be caused by a disability – "*they can only be original…..They are simply not set*

up to assimilate and learn an adult's knowledge".   Similarly he also emphasises the potential for good outcome, particular in the intellectually unimpaired, which at least in part results from "*their unswerving determination and penetrating intellectual powers [and] their narrowness and single mindedness*".

Like Kanner, Asperger felt that the condition he described was inborn - "*an explanation [for autism] in terms of exogenous causes must seem absurd*" - but he gives the starting age as prior to two years old as opposed to at birth.

Although Asperger's synthesis of the clinical characteristics of autistic psychopathy is less precise (and certainly less concise) than Kanner's, there is an impressive perceptiveness in his work. As Frith (1991) points out in her translation notes the paragraphs quoted above regarding social limitations are a very accurate description of poor mentalising, particularly when he refers to "*a genuine defect in their understanding of another person*". He also considers that the condition may be an "*extreme variant of male intelligence*", an idea since popularised by Simon Baron-Cohen and colleagues (Baron-Cohen 2002). He predates the idea of the autism spectrum when he comments that "*the characteristic manifestations of autism…are not at all rare in children, especially in their milder forms*" and indeed the broader autism phenotype when he discusses the "*related incipient traits in parents or relatives*". Finally he also notes similarities with other personality types, including Kretschmer's schizothyme, and expresses an intention to compare them with autistic psychopathy (although never did).

Evolution of the concept of autism: 1940s – 1950s

In the 20 years following Asperger's and Kanner's original descriptions there were a number of important occurrences relevant to the conceptualisation of autistic psychopathy. The first is that Asperger's writings went largely unnoticed by the psychiatric community. It has never really been clear why this was the case, although it is often attributed simply to language – Asperger published solely in German, whereas Kanner's descriptions dominated the English literature. Some have argued that Kanner was likely to be aware of Asperger's work but sought to suppress it, presumably for reasons of academic interest (Feinstein 2010). Certainly Kanner made no reference in any of his papers to Asperger's work, which seems unusual given that he is said to have been thorough in other aspects of his literature reviews and could speak German fluently (Chown 2012). However, it should be remembered that these were the days of the Second World War and transatlantic communication was difficult. Besides similar accusations could be levelled at Asperger in regard to his lack of reference to Sukhareva's paper, written in German 18 years before he published his account.

Although Kanner stated in his original paper that he regarded autism as a condition which was inborn he did comment on the aloof, academic and distant nature of the parents of the children he described. In the modern day we would regard this as a manifestation of the broader autism phenotype: a constellation of mild autistic-like traits seen in individuals who are genetically related to those with ASD, and indeed it appears that Asperger thought this was indeed the case. However, at the time that they were writing the spectre of Freud loomed large over the world of psychiatry and the idea of inborn

difficulties in interaction was anathema to a generation of psychiatrists raised in the psychodynamic tradition. Consistent with the zeitgeist, autism rapidly became regarded to be the consequence of cold parenting (Kanner 1949), a theory which persisted for many years.

Most relevant for the current discourse is that in the years following its first description autism came to be regarded as a form of very early onset childhood schizophrenia. In his 1943 paper Kanner mentions that some of the symptoms are similar to those of schizophrenia – "*extreme autism, obsessiveness, stereotypy and echolalia*" – but asserts their difference, primarily on the basis of age of onset and prognosis. As discussed earlier the concept of schizophrenia, particularly in the USA, was broadened considerably in the 1940s – 1960s by clinical descriptions of individuals felt to exhibit aspects of Bleuler's fundamental symptoms but who did not display classical positive symptoms. When one considers how the DSM-II diagnosis of schizophrenia was based upon aberrant concept formation, unusual emotional responsiveness, loss of empathy and bizarre behaviour it becomes rather easy to see how psychiatrists at this time viewed autism as a very early onset of schizophrenia which interferes with or causes a regression in development (Bender 1947). Kanner himself considered this issue in an address to the American Psychiatric Association where he reverses his previous position by concluding, "*Early infantile autism may therefore be looked upon as the earliest possible manifestation of childhood schizophrenia*"(Kanner 1949).

Finally, and related to the above, is that autism quickly went from being considered as a rare disorder to being a relatively common diagnosis. Children with known organic brain insults and many with intellectual disability and isolated signs of autism came to be regarded as autistic. Kanner himself later complained that in the 1950s,

"*It became a habit to dilute the original concept of infantile autism by diagnosing it in many disparate conditions which show one or more isolated symptoms found as a part feature of the overall syndrome… Almost overnight the country seems to be populated by a multitude of autistic children, and somehow this trend became noticeable overseas as well. Mentally defective children who displayed bizarre behaviour were promptly labelled autistic*" (Kanner 1973)

Evolution of the concept of autism: 1960s – 1970s

During the 1960s a number of authors began to return to Kanner's original theory that infantile autism and childhood onset schizophrenia were in fact separate conditions, with the latter showing continuity with adult schizophrenia (Rimland 1964; Rutter 1965). However, this was not confirmed until a group of landmark studies were published by Kolvin and colleagues in 1971 which essentially showed discrimination between the groups on the basis of their phenomenology, family history, parental personality, neurological function and intellectual ability.

In the first paper, they determined two groups of children with childhood psychoses: the first (infantile psychosis - IP) had an onset before the age of 3 and was characterised by

self-isolation and either catastrophic reactions to change or gross stereotypies; the second (late onset psychosis - LOP) began at between 5 and 15 years old and was characterised by Schneiderian first rank symptoms and disturbances to affect, motility and volition (Kolvin 1971).

Kolvin's second paper compared the phenomenology of the IP and LOP (Kolvin, Ounsted et al. 1971). They found that children with LOP were more likely to show an insidious onset and be "premorbidly odd" with social problems the most commonly noted – "*shyness, diffidence, withdrawal, timidity and sensitivity.*" The IP group were however, much more likely to show delayed achievement of milestones. They were also rated as being more impaired in their development of social relationships and their use of language. Abnormal preoccupations and resistance to change were found more frequently in the IP group, although both groups were equally affected with respect to ritualistic and perseverative behaviour. Thought disorder and hallucinations were both identified more commonly found in the LOP group. Features which were felt to have very high or high discriminatory power were gaze avoidance, abnormal preoccupations, disinterest in people, poor supervised play, stereotypies, echolalia, overactivity (all more common in IP) and hallucinations, disorder of content of thought, blunting of affect and incongruity of affect (all more common in LOP). The problem of ascertainment bias must be considered (and is mentioned by the authors); a group defined by Schneiderian first rank symptoms seems very likely to have greater levels of hallucinations than one which is not. However, it seems unlikely that this would account for all of the significant differences between the groups. Interestingly the authors do mention that some

individuals are clinically indistinguishable when the age of onset is not considered, particularly for those without florid positive symptoms.

The third paper considered the social background and family history of affected individuals (Kolvin, Ounsted et al. 1971). Social background of the parents differed between the groups with IP children tending to be from social class I and II and LOP children coming from social class IV and V. Social isolation was found to be non-significantly more common in the mothers of the children with LOP. Perhaps most importantly, an increase in the rate of adult schizophrenia was shown in the parents of the LOP group, but not the IP group, with no difference between the parents being seen in the rates of depression or neuroses.

In the fourth paper of the series Kolvin et al (1971) considered the personality types of the parents and found that introversion, oversensitivity and suspiciousness were more common in the parents of the LOP group than the IP group.

The fifth paper addressed a variety of associations within each group, summarised under the term cerebral dysfunction (Kolvin, Ounsted et al. 1971). They included obstetric events (ante-, peri- and post-natal complications), EEG recordings and neurological examination. Obstetric problems were more common in the IP group than the LOP group as was a low voltage EEG record. Overall 54% of IP cases and 31% of LOP cases showed some evidence of 'cerebral dysfunction' as defined by abnormalities in any of the domains above.

The final paper in the series identified that the IP group had a lower IQ than the LOP group (Kolvin, Humphrey et al. 1971).

This series of papers and others led to autism and schizophrenia being regarded as distinct disorders. Along with a general narrowing in the concept of autism which occurred around this time (Kanner 1973) this led to autism again being regarded as a rare condition and it remained so until the late 1970s and early 1980s

Evolution of the concept of autism: late 1970s - present

Folstein and Rutter's twin study in 1977 (Folstein and Rutter 1977) was one of the first studies to propose the theory that "autism is genetically linked with a broader range of cognitive disorders" (Feinstein 2010). However, it was the epidemiological study of Wing and Gould (1979) that really led to the birth of the spectrum concept of autism. They examined a selected group of children known to local statutory services as either disabled or behaviourally disturbed and divided them into 'socially impaired' and 'sociable [but] severely mentally retarded.' Of most relevance to the spectrum concept of autism, they then divided the socially impaired group using one of two methods: the type of their social impairment (aloof, passive or odd) or a history of typical autism. They found that the first of these methods gave the greatest separation on other clinical variables they measured and that the distribution of these variables suggested that "they formed a continuum of severity rather than discrete entities."

This idea that autism should not be regarded as a discrete condition was further popularised by Wings re-defining of Asperger Syndrome in 1981 (Wing 1981). The condition, Asperger Syndrome, which Wing describes, is derived from a combination of Asperger's own work and Wing's experience with 34 clinical cases. The clinical characteristics are mainly as Asperger described, except Wing adds to his accounts by describing a lack of imaginative play as well as some additional features which may be seen in the early years of life. She also disagrees with Asperger on two points. Firstly, she felt that her cases showed more abnormalities of language than described by Asperger (including language delay in around half of her cases). Secondly, she questioned the autistic intelligence that he emphasised:

"*Asperger described people with his syndrome as capable of originality and creativity in their chosen field. It would be more true to say that their thought processes are confined to a narrow, pedantic, literal, but logical, chain of reasoning. The unusual quality of their approach arises from the tendency to select, as the starting point for the logical chain, some aspect of a subject that would be unlikely to occur to a normal person who has absorbed the attitudes current in his culture. Usually the result is inappropriate, but once in a while it gives new insight into a problem.*"

Wing went on to discuss the differential diagnosis and classification of Asperger Syndrome. She reviewed Wolff's category of schizoid personality disorder of childhood (see Section 1.4) and, despite acknowledging that although people with Asperger Syndrome can clearly be regarded as having a schizoid personality, she somewhat

arbitrarily states that this is not a useful categorisation because "*this heading has no useful practical implications*" and "*there is not firm evidence of a special link between this syndrome and schizophrenia.*" Instead, she proposed that it forms part of a group of conditions, all characterised by a triad of impairments in social interaction, communication and imaginative activities. She highlighted that the relative severity of each aspect of this triad could differ in different people and that it could occur across individuals of different intellectual abilities. Asperger syndrome, she felt, would best be used to describe individuals who showed some autistic traits but "*who talk grammatically and who are not socially aloof.*" This conceptualisation of autism, not as a discrete disorder, but as part of a range of conditions laid the way for the modern ideas of the autism spectrum.

DSM-III

Prior to the development of DSM-III there was no mention of autism as a specific disorder. In DSM-I and DSM-II the closest diagnoses were "*schizophrenic reaction, childhood type*" and "*schizophrenia, childhood type*" respectively, both of which were described as presenting mainly with autism (as a symptom) (American Psychiatric Association 1952; American Psychiatric Association 1968). In DSM-III infantile autism was included under a new category, pervasive developmental disorders (American Psychiatric Association 1980).

The criteria for infantile autism in DSM-III were largely based upon Rutter's criteria, proposed in 1978 (Figure 1.9).

> 1. an onset before the age of 30 months
> 2. impaired social development that has a number of special characteristics and is out of keeping with the child's intellectual level
> 3. delayed and deviant language development that also has certain defined features and is out of keeping with the child's intellectual level
> 4. insistence on sameness, as shown by stereotyped play patterns, abnormal preoccupations, or resistance to change.

Figure 1.9: Criteria for the diagnosis of autism as proposed by Rutter (1978)

As well as infantile autism (which interestingly was divided into the full syndrome and the residual state; the latter represented people who had once met criteria for the full syndrome but no longer did, although still had some oddities of communication and social awkwardness) this category also included the diagnosis of "*childhood onset pervasive developmental disorder*" which had a later age of onset (30 months to 12 years) and included individuals with autistic features who do not show the full syndrome of infantile autism. A further diagnosis of "*atypical childhood onset pervasive developmental disorder*" was also included to capture individuals with aberrant development of social skills and language but who do not meet criteria for either of the other conditions.

DSM-III was published prior to Wing (1981), hence it is unsurprising that Asperger Syndrome is not specifically mentioned. However, the inclusion of childhood onset pervasive developmental disorder and its atypical form clearly indicate an acknowledgment that autism is part of a broader range of related conditions.

DSM-IV again utilises the umbrella category of pervasive developmental disorders, although now with five main subcategories: autistic disorder, Asperger disorder, non-specific pervasive developmental disorder (PDD-NOS), Rett's disorder and childhood disintegrative disorder (CDD) (American Psychiatric Association 2000). The first three conditions are all generally regarded as part of the autism spectrum whereas the classification of Rett's disorder and CDD remain unclear. The diagnostic criteria for autistic disorder and Asperger disorder are given in Figures 1.10 and 1.11 respectively. PDD-NOS is used when an individual shows a significant impairment in social interaction and either language or stereotyped behaviour but the criteria for other pervasive developmental disorders are not met.

The other two pervasive developmental disorders, Rett's disorder and CDD, are particularly characterised by the loss of previously acquired skills. Rett's disorder is a genetic disorder, caused by a mutation in the gene MECP2 on the X chromosome, although similar behavioural characteristics have also been seen in individuals with mutations in related genes. It is reported almost exclusively in females (affected males will usually die in utero). It is characterised by a period of typical development followed by a regression in several domains including social, motor and language skills. The diagnosis of Rett's disorder is now usually based upon a specific genetic test, as opposed to its behavioural characteristics, and it is largely regarded as a specific disorder which can cause autistic traits, as opposed to an autism spectrum disorder *per se*. Childhood disintegrative disorder (CDD), also called Heller's syndrome, is defined by a period of

typical development, of at least 2 but sometimes up to 10 years, followed by a rapid and severe loss of skills (over a period of months) in multiple domains, including social, motor, language, play and continence. Most children will develop a behavioural picture consistent with severe autism.

A) A total of six (or more) items from 1, 2, and 3 with at least two from 1, and one each from 2 and 3:
    1) qualitative impairment in social interaction, as manifested by at least two of the following:
        a) marked impairment in the use of multiple nonverbal behaviours, such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
        b) failure to develop peer relationships appropriate to developmental level
        c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
        d) lack of social or emotional reciprocity
    2) qualitative impairments in communication, as manifested by at least one of the following:
        a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
        b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
        c) stereotyped and repetitive use of language or idiosyncratic language
        d) lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level
    3) restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities as manifested by at least one of the following:
        a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
        b) apparently inflexible adherence to specific, non-functional routines or rituals
        c) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting or complex whole-body movements)
        d) persistent preoccupation with parts of objects

B) Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: social interaction; language as used in social communication; or symbolic or imaginative play.

C) The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder.

Figure 1.10: DSM IV-TR diagnostic criteria for autistic disorder

A) Qualitative impairment in social interaction, as manifested by at least two of the following:
    1) marked impairment in the use of multiple nonverbal behaviours, such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
    2) failure to develop peer relationships appropriate to developmental level
    3) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest to other people)
    4) lack of social or emotional reciprocity

B) Restricted, repetitive, and stereotyped patterns of behaviour, interests, and activities, as manifested by at least one of the following:
    1) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
    2) apparently inflexible adherence to specific, non-functional routines or rituals
    3) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
    4) persistent preoccupation with parts of objects

C) The disturbance causes clinically significant impairment in social, occupational, or other important areas of functioning.

D) There is no clinically significant general delay in language (e.g., single words used by age 2 years, communicative phrases used by age 3 years).

E) There is no clinically significant delay in cognitive development or in the development of age-appropriate self-help skills, adaptive behavior (other than in social interaction), and curiosity about the environment in childhood.

F) Criteria are not met for another specific pervasive developmental disorder or schizophrenia.

Figure 1.11: DSM-IV-TR diagnostic criteria for Asperger's disorder

The future for the autism spectrum: DSM-5

Amid much controversy (McPartland, Reichow et al. 2012; Swedo, Baird et al. 2012) the soon to be published DSM-5 will contain a quite different categorisation system for autism spectrum disorders. The category of pervasive developmental disorders will be discarded and replaced with "*autism spectrum disorders*". There will be no specific sub-diagnoses included under this category: i.e. autistic disorder, Asperger disorder and PDD-NOS will all be subsumed under the single diagnosis, autism spectrum disorder. Clinicians will then be encouraged to add separate diagnostic specifiers to capture the severity, onset, cognitive abilities, known aetiologic factors and any associated conditions.

As well a change in classification the criteria required to be met for a diagnosis of an autism spectrum disorder differ from those previously employed for pervasive developmental disorders. The social and communication domains will be combined to form one new domain along with restricted repetitive behaviour and interests (Figure 1.12).

A) Persistent deficits in social communication and social interaction across contexts, not accounted for by general developmental delays, and manifest by all 3 of the following:
    1. Deficits in social-emotional reciprocity
    2. Deficits in nonverbal communicative behaviours used for social interaction
    3. Deficits in developing and maintaining relationships

B) Restricted, repetitive patterns of behaviour, interests, or activities as manifested by at least two of the following:
    1. Stereotyped or repetitive speech, motor movements, or use of objects
    2. Excessive adherence to routines, ritualized patterns of verbal or nonverbal behaviour, or excessive resistance to change
    3. Highly restricted, fixated interests that are abnormal in intensity or focus
    4. Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment;

C) Symptoms must be present in early childhood (but may not become fully manifest until social demands exceed limited capacities

D) Symptoms together limit and impair everyday functioning.

Figure 1.12: Proposed DSM-5 diagnostic criteria for autism spectrum disorder

DSM-5 will also introduce a new diagnosis of social communication disorder. Although classified under communication disorders, not autism spectrum disorders, it is a clearly related concept (Figure 1.13).

A) Persistent difficulties in the social use of verbal and nonverbal communication as manifest by
      deficits in the following:
      1) Using communication for social purposes, such as greeting and sharing information, in a
      manner that is appropriate for the social context;
      2) Changing communication to match context or the needs of the listener, such as speaking
      differently in a classroom than on a playground, communicating differently to a child than to
      an adult, and avoiding use of overly formal language;
      3) Following rules for conversation and storytelling, such as taking turns in conversation,
      rephrasing when misunderstood, and knowing how to use verbal and nonverbal signals to
      regulate interaction;
      4) Understanding what is not explicitly stated (e.g. inferencing) and nonliteral or ambiguous
      meanings of language, for example, idioms, jokes, metaphors and multiple meanings that
      depend on the context for interpretation.

B) Deficits result in functional limitations in effective communication, social participation, social
      relationships, academic achievement, or occupational performance.

C) Onset in the early developmental period (but deficits may not become fully manifest until social
      communication demands exceed limited capacities).

D) Deficits are not better explained by low abilities in the domains of word structure and grammar, or
      by intellectual disability, global developmental delay, Autism Spectrum Disorder, or another
      mental or neurologic disorder.

Figure 1.13: Proposed DSM-5 diagnostic criteria for social communication disorder

1.4: OVERLAPS OF ASD AND SSD IN THEIR CONCEPTUAL DEVELOPMENT

Autism spectrum and schizophrenia spectrum disorders have an intertwined history,
arising first out of a common terminology and then from the idea that they were both
forms of the same condition. Although the work of Kolvin and others in the late 1960s
and 1970s drew a distinction between autism and schizophrenia, the distinction between
the broader spectrum conditions remains less clear.

In the early descriptions of relatives of people with schizophrenia, traits which would
now be regarded as similar to those found in autism spectrum disorders are mentioned

with reasonable frequency and by several different authors, e.g. unsociability, stubbornness, logical, over-pedantic, literal-mindedness with a preference for office work and fixed rules (Kraepelin 1919; Kretschmer 1925; Kallmann 1938; Bleuler 1950). Similarly, the descriptions by Hoch and Rado of people with pseudoneurotic schizophrenia and schizotypal conditions respectively also contain features which are reminiscent of autistic spectrum traits, albeit mixed with many other features and described in the, at times slightly pejorative although rather descriptive, language of 1950s psychodynamic thinking:

"*..one often finds rigidity in thinking, stereotypy of thought and perseveration of thought. In such circumstances, the thought process and goal are adamantly pursued despite clear and necessary indications to abandon them. Interruptions, necessary delays and appropriate shifts are not tolerated…..specific stereotyped sequences of associations may be pursued repeatedly and endlessly or to the point of exhaustion. In many instances, evaluation of the logicality of the on-going thought process and the thought goal is disturbed by doubting and indecisiveness with the result that action is often blocked…..The patient attempts to function according to stereotyped labels and fixed formulas with the conviction that all problems can be solved by the intellect. There is an emphasis on absolute values, "black and white" standards, while discounting obvious breaches, ridiculous paradoxes and impossible dilemmas.*" (Hoch and Cattell 1959)

"*Schizotypes lack the feel for the simple pleasures, the affectionate give-and-take of daily life. In lieu of immediate emotional grasp the baffled patient presses his intellect into*

service, as if trying to pick up something at a distance with lazy tongs. For the spontaneous pleasurable response he lacks he substitutes mechanical limitations. If highly sophisticated, he may ridicule the conventional forms of affectionate behaviour, dissecting and examining them as though they were the technological performance of a machine" (Rado 1953)

Kanner too recognised the clinical overlap between infantile autism and schizophrenia (Kanner 1949), while Asperger indicated the need for studies to determine the relationship between his personality disorder and Kretschmer's schizothymia (Asperger 1991). When re-describing Asperger syndrome, Lorna Wing explicitly stated that "*there is no question that Asperger syndrome can be regarded as a form of schizoid personality*" (Wing 1981), a comment made with regard to the work of Sula Wolff who over the course of 30 years described almost 150 children with a condition she called schizoid personality disorder of childhood (see below). However, Wing felt this was unhelpful as the terms schizoid and personality disorder were too broadly defined to be useful and implied a link to schizophrenia which was unproven.

Wolff first reported a case series of children with schizoid personality disorder of childhood in an oral address in 1964 (Wolff 1964), although the first published account was in 1979 (Wolff and Barlow 1979). Unaware of Asperger's cases in 1964, Wolff chose the term schizoid for the children she encountered as the symptoms with which they presented closely matched those of adults with the diagnosis of schizoid personality disorder. By 1979, she was familiar with Asperger's work and commented that the

children were "identical in all aspects with those described by Asperger" but chose to continue with the term schizoid (Wolff and Barlow 1979). It is important to note that at the time she was initially writing schizoid was used in the broader, pre DSM-III, sense and she later commented that in modern diagnostic terms they children could be described as showing schizotypal personality disorder or "Cluster A personality disorder" of childhood (Wolff and McGuire 1995) (Cluster A includes the modern personality disorders schizoid, schizotypal and paranoid). The operationally defined characteristics of schizoid personality disorder of childhood were: solitariness, impaired empathy and emotional detachment, increased sensitivity, rigidity of mental set and an unusual style of communication (Wolff and Chick 1980).

Recognising the similarities of their condition with Kanner's autism, Wolff and Barlow (1979) compared a group of children with schizoid personality disorder of childhood, a group with autism and a group of control children. They found that the children with autism showed greater perseveration than the schizoid group, whereas the schizoid group used fewer emotional terms to describe pictures of their mother, although the latter was not statistically significant. On other tests the schizoid children generally scored intermediate between the children with autism and the controls.

Shortly following the first published description of schizoid personality disorder of childhood, Wing published her paper which redefined Asperger syndrome as a form of autism (Wing 1981) and schizoid personality disorder of childhood gradually became considered to be part of the autism spectrum. However, Wolff argued on several

occasions (Wolff 1991; Wolff and McGuire 1995) that the children that Asperger described, like those she diagnosed with schizoid personality disorder, were less severely impaired than those with Asperger syndrome as defined by Wing (1981)and others (Tantam 1988; Gillberg 1989) who were more clearly autistic in nature. She also pointed out that, in contrast to children with Wing's Asperger syndrome, those who she diagnosed as schizoid had active but unusual fantasy lives, a high chance (75%) of meeting criteria for DSM-III schizotypal personality disorder as adults (Wolff, Townshend et al. 1991) and a 5-10 times increased risk of schizophrenia compared to the general population (Wolff 1992).

Overall, Wolff felt that the children she described had a milder variant of Wing's Asperger syndrome, but that the links with schizophrenia should be recognised; she therefore proposed that the disorder should be named schizoid/Asperger syndrome (Wolff 1995). She also suggested that the development of a schizoid personality may represent a genetic vulnerability state to both autism and schizophrenia but that additional different genetic and environmental factors act to cause the more serious disorders (Wolff and McGuire 1995). Although the diagnostic label of schizoid/Asperger syndrome was not adopted and Asperger syndrome is now firmly rooted in the autism spectrum, the recognition of less severely affected individuals as falling within the diagnosis of Asperger syndrome and Wolff's proposal of a partial overlap with the schizophrenia spectrum are currently very much in vogue (King and Lord 2011; Stone and Iguchi 2011).

Although long recognised, the modern concepts of autism spectrum disorders and for schizophrenia spectrum disorders began to be formalised in DSM-III. It is important to note that the two categories arose out of largely separate processes; the criteria for schizotypal personality disorder were validated in adults and were derived from the Danish Adoption Study with one of the primary objectives being its distinction from borderline personality disorder (Spitzer, Endicott et al. 1979); the criteria for infantile autism were validated in children and derived from Rutter's 1978 criteria which, although he considers the possible overlap with schizophrenia, do not take into account the broader schizophrenia spectrum disorders (Rutter 1978).

DSM-III does list schizotypal personality disorder as a possible differential diagnosis for childhood onset pervasive developmental disorder, with the latter stated to show more severe disturbance in social relations as well as aberrant motor movement, self-mutilation and inappropriate affect. However, the concepts of both the autism and schizophrenia spectrums have developed further since this time and this has not had the effect of clearly delineating them. Autism as a diagnosis has expanded to cover milder forms of social impairment with less disturbed behaviour, making the differences from schizotypal personality disorder described above less pertinent. The formalisation of autism as a spectrum in DSM5 seems likely only to continue this process, with the addition of social communication disorder (albeit not as part of the autism spectrum) a potential further complicating factor. The inclusion of empathy deficits as a specific part of the criteria for schizotypal personality disorder is likely to have a similar effect of increasing the overlap between these diagnoses.

1.5: CONCLUSION

Autism and schizophrenia have largely arisen out of different conceptual frameworks. Despite this, there has always been noticeable overlaps in their phenomenology, particularly in the case of the spectrum disorders, ASD and SPD. This has increased in recent years as the conceptions of these disorders has evolved, particularly in the case of ASD, which now encompasses a much greater range of disability than in the past. It has therefore become unclear whether we can distinguish these conditions from each other, indeed are we even correct to classify them separately? There is a need for a study to consider the relationship between ASD and SPD, not only in regard to their clinical features, but also including biological measures which may provide more objective information about their relationship. As a first step towards this, the next chapter will review the existing literature to identify the potential shared and discriminating features of these spectrum conditions.

Chapter 2

Review of existing literature relevant to the potential shared and discriminating

features of the autism and schizophrenia spectrums

2.1: INTRODUCTION

Other than Wolff's work, interest in the relationship between autism and schizophrenia waned considerably following Kolvin's series of papers. However, a number of recent authors have again started to question this relationship, suggesting that the two disorders may be more closely related than previously thought (Nylander, Lugnegård et al. 2008; Rapoport, Chavez et al. 2009; Padgett, Miltsiou et al. 2010; King and Lord 2011; Stone and Iguchi 2011). Two prominent over-arching theories of the relationship between autism and schizophrenia have been put forward, both based around predominantly genetic hypotheses.

In 2008, Crespi and Badcock (2008) proposed that autism and schizophrenia represented diametrically opposite conditions mediated by alterations in genomic imprinting, an epigenetic phenomena occurring in about 1% of human genes leading to either the maternal or paternal allele being differentially expressed. They suggest that people with autism have biases towards paternally expressed genes while those with schizophrenia have a bias towards maternally expressed genes. Their hypothesis rests upon evolutionary conflict theory and its relationship to genomic imprinting. Essentially this theory states that in a society where multiple males may father offspring from one female, paternally expressed genes are associated with gaining evolutionary fitness at the expense of the mother (e.g. through overgrowth), whereas maternally expressed genes are associated with traits which are beneficial to the mother (such as reduced growth) thereby allowing her to survive and produce more offspring (Haig 2000). In support of their hypothesis, Crespi and Badcock cite a great deal of evidence suggesting that autism and

schizophrenia are opposed across a broad range of features: e.g. increased brain size in autism / reduced brain size in schizophrenia; hypomentalising in autism / hypermentalising in schizophrenia; reduced imagination in autism / increased imagination and delusions in schizophrenia; reduced language skills in autism / auditory hallucinations in schizophrenia; increased local processing in autism / increased global processing in schizophrenia (Crespi and Badcock 2008) . However, a number of criticisms of their hypothesis are possible: the conflict theory of genomic imprinting is in itself controversial (Keverne and Curley 2008); which character traits are maternally beneficial and which are paternally beneficial is far from clear; no mechanism for why the imbalance might occur is advanced by their theory; and their use of evidence is somewhat selective (Keller 2008).

Others, noting overlaps in some of the genes implicated in the disorders and in their clinical features, have proposed that instead of being diametrically opposed disorders, autism and schizophrenia actually represent different points on a broad spectrum of neurodevelopmental disorders (Carroll and Owen 2009; Craddock and Owen 2010; Cross-Disorder Group of the Psychiatric Genomics, Smoller et al. 2013). This would predict that the disorders should show at least some overlap in their features and that these should show common pathophysiological mechanisms, although one could speculate that the nature of gene-gene interactions would complicate this picture somewhat.

As the preceding chapter has outlined, the relationship between autism and schizophrenia is especially unclear when one considers the spectrum disorders, ASD and SPD, which contain many overlapping features in their historical descriptions, current definitions and proposed future developments to their classification. Research examining this area is therefore timely and indeed necessary. In order for any such project to shed light on the similarities and differences between these conditions, it will be important to consider both clinical measures and more objective measures of brain function, such as those derived from neuropsychology and neuroimaging. The existing literature in these fields which pertains to ASD and SPD is therefore reviewed below.

2.2: CLINICAL CHARACTERISTICS

As alluded to in Chapter 1, even a fairly cursory review of the current DSM-IV and proposed DSM-5 diagnostic criteria for autism spectrum disorders (ASD) and schizotypal personality disorder (SPD) reveal potential overlaps between the disorders. Both may be associated with idiosyncratic communication, social withdrawal, a lack of social understanding and unusual affect. Even the restricted, repetitive behaviours which seem to more characteristic of ASD, can be found in the diagnostic criteria for SPD in the form of the stereotyped speech mentioned in DSM-5 and potentially also the eccentric behaviour criterion. These potential clinical overlaps are further confounded when one considers the psychiatric comorbidities which are known to be associated with both conditions. Anxiety in particular is known to be associated with both ASD and schizotypal traits (Weisbrot, Gadow et al. 2005; Lewandowski, Barrantes-Vidal et al.

2006), as are obsessive-compulsive phenomena (Poyurovsky and Koran 2005; Leyfer, Folstein et al. 2006) – this especially renders the presence of repetitive behaviour to distinguish the spectrums less useful.

Perhaps the clearest distinguishing feature between autism and schizophrenia is the differential age of onset (typically in infancy for autism and in late teenage years / early adulthood for schizophrenia). Indeed age of onset was how Kolvin originally delineated his groups in his detailed comparison of the disorders (Kolvin 1971). However, it is now recognised that, although the impairments in ASD begin in infancy, they may not become apparent until later in life when social demands exceed abilities (American Psychiatric Association 2013). In addition, although schizophrenia has a clear onset which is usually following childhood, the course of schizotypal personality disorder is unknown. In particular, we do not know at present whether SPD is present from a very early age or whether there is a decline in function in late adolescence. Certainly, studies of people at risk of schizophrenia for genetic reasons have shown that, although some individuals are premorbidly relatively unimpaired, others show high levels of schizotypal traits as adolescents (Johnstone, Ebmeier et al. 2005). Indeed, even studies of infant relatives of people with schizophrenia have found higher levels of disturbance to social functioning than controls (Asarnow 1988).

A number of other studies have considered the relationship between the autism and schizophrenia spectrums from a clinical perspective and these are reviewed below. A variety of different and overlapping study designs have been used. These can be broadly

divided (with some overlap) into: direct comparisons of autism and schizophrenia; studies which have examined the rates of psychotic disorders in people with ASD and vice versa; studies which have considered the rates of schizotypal traits in populations with ASD and vice versa; and studies which have examined the relationship between autistic and schizotypal traits in non-clinical samples. To the author's knowledge there has been no previous study directly comparing the clinical features of ASD with SPD

2.2.1: Comparisons of ASD and schizophrenia

Kolvin's series of papers discriminating autism from childhood schizophrenia have been reviewed in Chapter 1. Although many features were identified that differed between the groups there were also significant overlaps in the clinical picture. Some of the features which were to discriminate poorly or not at all between the groups included: speech delay, pronominal reversal, thought disorder, poor mixing with peers, resistance to change, ritualistic behaviour, unpredictable response to sounds, perplexity, mannerisms, ambitendency, ambivalence and jerkiness of movement (Kolvin, Ounsted et al. 1971).

Konstantareas et al (2001) found no difference in the rates of negative symptoms between individuals with autism and those with schizophrenia. Positive symptoms were more common in the schizophrenia group, although they also identified the presence of at least one positive symptom in 35% of their autism group.

Rumsey et al (1986) compared the type and degree of thought disorder in adults with autism to those with schizophrenia. They found a higher prevalence of poverty of speech

in the autism group, whereas the schizophrenia group showed more positive thought disorder (derailment, illogicality and loss of goal). The groups did not differ on their levels of affective flattening. Similarly, Dykens et al (1991) found higher levels of poverty of speech in people with autism compared to those with schizophrenia, but less illogicality.

More recently Spek et al (2010) compared 21 individuals with autism to 21 individuals with schizophrenia using self-reported measures of autistic and schizotypal traits (the autism spectrum quotient (AQ - (Baron-Cohen, Wheelwright et al. 2001)) and the schizotypal personality questionnaire (SPQ - (Raine 1991)). They found that individuals with autism rated themselves as more impaired on the AQ with regard to social skill, attention switching and communication, with no difference between the groups in attention to detail or imagination. On the SPQ, the schizophrenia group rated themselves as more impaired with respect to positive schizotypy, there was a trend towards greater negative schizotypy in the ASD group and no difference between the groups with respect to disorganisation. In terms of discrimination, only social skill (on the AQ) and positive schizotypy (on the SPQ) usefully discriminated the groups. They also found slightly different relationships between the subscales in each group, such that negative schizotypy correlated negatively with attention to detail in the schizophrenia group, whereas in the autism group it correlated positively with difficulty switching attention – this they interpret as potentially meaning that negative symptoms in the two groups reflect different processes.

In summary, studies which have directly compared ASD and schizophrenia show clinical overlaps between the groups, particularly with regard to negative and disorganised symptoms. Positive symptoms are more common in schizophrenia, but also occur reasonably frequently in ASD, although the lack of typically developing control groups in the studies reviewed means that it is unclear whether this is to a greater degree than the general population.

2.2.2: Prevalence of psychotic disorders in ASD

The majority of studies which have considered comorbid psychiatric disorders in ASD have examined children; this has implications when one is considering the relationship with psychosis as most people will not become unwell until late adolescence / early adulthood. Regardless, some studies have reported increased rates of psychotic symptoms and psychotic disorders in children with ASD, whereas others have not. De-Bruin et al (de Bruin, Ferdinand et al. 2007) examined 6-12 year old children with PDD-NOS and found high levels of psychiatric comorbidity. Although none of the children met criteria for schizophrenia, hallucinations and delusions were found in 5% and 3% respectively. Similarly, psychotic symptoms (although not diagnoses) were found in 12% of children and adolescents (mean age 12) with ASD by Caamano et al (2013) compared to none of the controls. In keeping with this, Joshi et al (2010) found that 20% of the individuals with ASD referred to a paediatric psychopharmacological centre met criteria for a psychotic illness, compared to 12% of other referrals.

In contrast to the above, Gjevik et al (2011) found that only 1.5% of their sample (n=71, aged 6-18 years old) met criteria for a psychotic illness. Similarly, in a large database study of 4343 children with ASD, 0.5% of parents reported their children having received a diagnosis of schizophrenia (Rosenberg, Kaufmann et al. 2011). Leyfer et al (2006) and Mattila et al (2010) found no cases of schizophrenia in their samples of children and adolescents with autism (109 and 50 individuals respectively).

In addition to chance, differences between the studies mentioned above may reflect differences in how they were recruited – e.g. the 20% figure of Joshi et al (2010) likely reflects that their children had been referred specifically for evaluation of their suitability for psychotropic medication. It should also be noted that ascertainment bias may well have inflated the figures as none were population studies, i.e. all individuals had to at least opt-in and were usually clinical referrals.

Fewer studies have specifically investigated the rates of psychotic disorders in adults with autism. Konstantareas and Hewitt (2001) found that 50% of their sample of 14 individuals with autism also met diagnostic criteria for a schizophrenia, disorganised type with negative symptoms. Hofvander et al (2009) studied 122 adults with ASD who were referred to specialist centres for diagnostic assessments and found that 12% met criteria for a psychotic illness. In addition they found rates of paranoid, schizoid and schizotypal personality disorders of 19%, 21% and 13% respectively. Previously, members of the same group had reported rates in a smaller sample of 26%, 32% and 23% respectively (Anckarsäter, Stahlberg et al. 2006).

Overall the evidence regarding the rates of psychotic disorders in ASD is unclear. Ascertainment bias and the tendency to study children who are below the usual age of onset of schizophrenia make it difficult to draw any firm conclusions as to whether there is actually an increased rate of schizophrenia or other psychotic diagnoses in ASD.

2.2.3: Schizotypal / psychotic traits in ASD

Craig et al (2004) found that a group of people with Asperger Syndrome scored more highly than controls, but less than people with schizophrenia, on the Paranoia Scale (Fenigstein and Vanable 1992), a measure of paranoid ideation. Both groups also showed deficits in their ability to mentalise (see Chapter 2.3.5) but the schizophrenia group also displayed a tendency to make external attributions for negative events (essentially to blame others for negative events) which the authors suggest shows differences in the mechanisms of paranoia in the groups. Similarly, Blackshaw et al (2001) also found higher rates of paranoia in people with Asperger syndrome compared to controls but no difference in causal attributions (in contrast to previous findings in schizophrenia). Pinkham et al (2012) compared paranoid symptoms between 101 individuals divided into four groups (ASD, schizophrenia with paranoia, schizophrenia without paranoia and controls). They found no difference in the overall level of paranoia between the ASD and schizophrenia with paranoia groups, both of whom scored more highly than the controls of the schizophrenia without paranoia groups. However, they then went on to use discriminant correspondence analysis to identify factors which best discriminated between the groups. Three factors were identified: Paranoia (70% of the

variance), cynicism (16% of the variance) and insightful acknowledgement (13% of the variance).   They found that individuals with schizophrenia and paranoia separated from individuals with Asperger syndrome on the basis of their scores on the cynicism factor, but not the others and, consistent with Craig et al (2004) and Blackshaw et al (2001), interpret this as evidence that the nature of the paranoia differs between the groups.

Consistent with the comparative studies of Dykens et al (1991) and Rumsey et al (1986), Solomon et al (2008) found increased loosening of associations, illogical thinking and poverty of content in a group of adolescents with ASD relative to controls. The level of thought disorder in the ASD group was related to anxiety and reduced executive control. Similarly, Van der Gaag (2005) found high rates of illogical thinking and loosened associations in individuals with autism compared to controls and these were related to lower verbal IQ.

Barneveld et al (2011) found that adolescents with ASD, showed higher levels of positive, negative and disorganised schizotypal traits (as measured by the SPQ) than controls. The levels of negative, positive and disorganised schizotypy were said to be equivalent to those seen in first episode schizophrenia. They also found correlations between negative schizotypy and greater impairment on the AQ domains of social skills, attention switching, communication and imagination; positive schizotypy and impaired attention switching; and disorganised schizotypy and attention switching and communication.

In a large population of 147 children with ASD, Gadow (2012) found that individuals with ASD showed higher levels of schizoid personality traits than non-ASD child psychiatry outpatients. Levels of disorganised behaviour and negative symptoms were also higher in the ASD group but only in those with comorbid ADHD (who scored more highly than controls with and without ADHD). In a further paper Gadow describes the relationship between autistic and schizotypal symptoms in each group divided by ADHD status and found that, in general, disorganised thinking and negative symptoms correlated with autistic traits, although there were condition specific and informant specific effects (Gadow 2013).

In summary, there is strong evidence that individuals with ASD show higher levels of schizotypal traits than controls. Although this is most pronounced for negative and disorganised features, there also exist increased rates of positive schizotypal traits in ASD; indeed, in one study these were even to the same level as that seen in schizophrenia. There is some evidence, albeit fairly weak, that positive symptoms may relate to different underlying psychological mechanisms in people with ASD than in schizophrenia.

2.2.4: Autistic traits in schizophrenia and schizotypal personality disorder

Sheitman et al (2004) examined 21 individuals with chronic, treatment resistant schizophrenia and correlated their scores on the Autism Behaviour Checklist (Krug, Arick et al. 1980) with those on the Positive and Negative Syndrome Scale (Kay,

Fiszbein et al. 1987). They found that autistic traits correlated positively with severity of negative symptoms and general symptoms, but not with positive symptoms.

As described above, Spek et al (2010) found associations between negative symptoms and slightly different subscales of the AQ depending on whether individuals had a diagnosis of autism or schizophrenia. In this study, individuals with schizophrenia showed similar levels of impairment between people with autism and those with schizophrenia in terms of attention to detail or imagination as measured by the AQ. Although the autism group scored more highly than the schizophrenia group on the other subscales (social skill, attention switching and communication) the scores on these for the schizophrenia group were higher than those generally reported for typically developing individuals (Baron-Cohen, Wheelwright et al. 2001).

To the author's knowledge there has only been one study of autistic traits in a population with diagnosed schizotypal personality disorder (Esterberg, Trotman et al. 2008). This group examined 35 adolescents with SPD using the Autism Diagnostic Interview (ADI – R – (Rutter, Le Couteur et al. 2003)) and compared them to 38 adolescents with other personality disorders and to 48 controls. They found that the SPD group had the highest levels of social impairment and unusual interests and behaviours in childhood and currently, but no differences were seen in communication impairments. Within the SPD group, autistic traits and negative symptoms correlated significantly but this was not the case in the other groups, although the authors do not report if this group x symptom interaction is significant. Autistic traits and positive symptoms did not correlate

significantly in any of the groups when considered separately. This study also identified that higher levels of autistic traits did not predict transition to psychosis over 3 years in people with SPD, which the authors interpret as meaning that autistic traits are not simply representative of greater schizotypy. An alternative explanation would be that autistic traits actually represent higher negative schizotypy which is not in itself a predictor of later psychosis.

Overall therefore there is some evidence for increased autistic traits in SPD and schizophrenia compared to controls, although only a limited number of studies have explicitly examined this area.

2.2.5: Studies of non-clinical samples

Several authors have taken the approach of looking at the association between schizotypal and autistic traits in non-clinical samples, primarily psychology students. All have essentially reported similar results: positive correlations across a range of schizotypal and autistic traits, especially, but importantly not limited to, those domains which capture social impairments (Hurst, Nelson-Gray et al. 2007; Claridge and McDonald 2009; Russell-Smith, Maybery et al. 2011; Wakabayashi, Baron-Cohen et al. 2012).

2.2.6: Summary of clinical studies

Overlaps between autistic and schizotypal / psychotic traits are found in almost every study which has considered them. The overlap is particularly strong for negative

symptoms / social impairments, with disorganised symptoms and thought disorder also commonly found in both groups. In addition, positive symptoms are also related to the levels of autistic traits in people with ASD and both also occur more frequently in individuals with ASD than in controls, although at lower levels than is found in schizophrenia. There is a gap in the present literature which concerns a direct comparison of individuals with ASD to those with SPD. Inferences from the above would suggest that such a study would at least show significant overlaps between the groups in negative symptoms and social impairments, and quite possibly in regard to the other features of the disorder; indeed it may not be possible to distinguish the conditions at all.

Two possible explanations present themselves for the overlap between schizotypal and autistic traits. Firstly it is possible that they are different phenomena, arising from separate mechanisms, which are simply difficult to distinguish clinically. Alternatively, they may represent a shared pathophysiological process. The findings from Spek et al (2010) and Pinkham et al (2012) are slightly suggestive that the former is correct for negative symptoms and positive symptoms respectively, although they are not conclusive.

2.3: BRAIN FUNCTIONAL CHARACTERISTICS

Neuropsychological studies of schizophrenia have a long history with a wide range of cognitive domains highlighted as potentially involved. These include processing speed,

episodic memory, executive function (including working memory, set-shifting, inhibition, planning), sustained attention, social cognition, motor speed, verbal fluency, perceptual processing and general intellectual ability (Fioravanti, Carlone et al. 2005; Couture, Penn et al. 2006; Dickinson, Ramsey et al. 2007). The widespread nature of the cognitive impairments in schizophrenia means that no single cognitive process is generally held to account for all of the symptoms of the condition although it has been proposed that specific cognitive deficits are associated with particular symptom domains (Frith 1992). Studies in relatives of people with schizophrenia and in those with schizotypal personality disorder tend to show deficits in many of the same cognitive processes as are in seen in schizophrenia, albeit less pronounced, and with sparing of motor abilities. (Siever and Davis 2004; Dickinson, Ramsey et al. 2007).

The neuropsychological theories of ASD can be summarised under three major domains: executive dysfunction, weak central coherence and impaired social cognition (Sanders, Johnson et al. 2008). Similar to schizophrenia, recent thinking in the ASD field has moved away from the idea that any single one of these cognitive theories can account for all of the symptoms of autism (Happé and Frith 2006; Happé, Ronald et al. 2006). However, each of these domains has also been examined in schizophrenia and to a lesser extent in schizotypal groups; they therefore represent a useful way in which to consider potential shared and discriminating features of the spectrums.

2.3.1: Neuropsychological studies of executive dysfunction

Executive function is an umbrella term used to describe a set of brain functions that are involved in the regulation and control of other cognitive processes to accomplish a particular goal (Elliott 2003). There is no general agreement on what exactly constitutes executive function, although planning, attention, working memory, inhibition, set-switching and generativity (the generation of novel ideas and concepts) are often included (Hill 2004; Alvarez and Emory 2006). Almost invariably these functions are held to involve the prefrontal lobe although this is probably overly simplistic; although the prefrontal lobe plays a key role, intact connectivity with other cortical and subcortical regions is required for successful executive function (Alvarez and Emory 2006; Kenworthy, Yerys et al. 2008).

Executive function in ASD

Interest in executive dysfunction in ASD arises originally from the clinical observations of repetitive and stereotyped behaviours which characterise the disorder (Happé and Frith 1996; Hill 2004). No exact or specific pattern of executive difficulties characterising ASD has been found, a fact which has been attributed to the difficulties measuring executive function in general and those more specific to ASD. General problems include the long and varied developmental trajectory of executive functions, the lack of agreement of what executive function actually is and difficulties in measuring an inherently complex construct (e.g. should we consider it a unitary concept or divide it into component parts). Problems more specific to ASD include confounding due to task modality (e.g. visuospatial versus verbal) and from the social nature of conducting any

face to face test (computer studies tend to show fewer deficits than those administered by humans), high levels of psychiatric comorbidity and the complicating effects of general intellectual level (Kenworthy, Yerys et al. 2008). As might therefore be expected, studies have identified impairments in people with ASD across all the domains of executive function listed above (Kenworthy, Yerys et al. 2008), although there is some evidence that there is sparing of sustained attention (Goldstein, Johnson et al. 2001), verbal working memory (Koshino, Carpenter et al. 2005; Williams, Goldstein et al. 2005; Williams, Goldstein et al. 2006) and possibly also inhibition (Hill 2004).

Executive function in the schizophrenia spectrum

Investigating executive function in schizophrenia is beset by the same problems as outlined above, with the addition of the confounding factors of medication, state versus trait effects and illness progression. Studies of schizotypal personality disorder do not usually have these additional problems as individuals do not show discrete episodes of illness and do not usually take medication; whether they show progression of cognitive deficits is unknown. There are however many fewer studies of SPD than schizophrenia meaning that less definite conclusions can be drawn. Nevertheless, similar to the findings in ASD, neuropsychological studies of SPD have found impairments across multiple domains of executive function including working memory (verbal and visuospatial), sustained attention, set-shifting and planning (Siever and Davis 2004), although again findings are not consistent (Matsui, Yuuki et al. 2007). Studies of individuals rated as high on schizotypy on self-report measures have also identified deficits in sustained attention, working memory and set-shifting (Giakoumaki 2012).

Executive impairments in schizophrenia (and possibly therefore also in SPD) appear to be particularly associated with negative and disorganised symptoms, as opposed to positive ones (Dibben, Rice et al. 2009).

Interestingly, the generation of novel ideas may be a potential outlier in respect to the otherwise broad deficits in executive function found in schizotypal individuals. There is a consistent association found between creativity and schizotypal traits in the general population (Nelson and Rawlings 2010) and this has been proposed to account for the evolutionary persistence of schizophrenia (Burch, Pavelis et al. 2006; Nettle and Clegg 2006). However in schizophrenia, studies have shown impairments in verbal fluency (Dickinson, Ramsey et al. 2007) and ideational fluency (Abraham, Windmann et al. 2007) compared to controls. One study of verbal fluency has been conducted in people with SPD and deficits were noted (Dickey, Morocz et al. 2010), suggesting that SPD, like schizophrenia, may represent too severe a phenotype to confer any advantage in this regard.

Studies comparing executive function between the autism and schizophrenia spectrums
Unfortunately there are no studies which have directly compared executive function in individuals with ASD to those with SPD. Perhaps the closest is a study by Bolte et al (2006) which compared central coherence and executive function in the parents of people with autism to the parents of people with schizophrenia. In terms of executive function, they tested set shifting using the Wisconsin Card Sorting Test (WCST) and planning using the Tower of Hanoi and the Trail Making Test and did not find any significant

difference between the groups.   Unfortunately they did not measure autistic or schizotypal traits in the relatives therefore how impaired these groups were is unknown, but it seems reasonable to assume that not all met criteria for a broader spectrum disorder. Barneveld et al (Barneveld, de Sonneville et al. 2013) found that increasing impairment in response inhibition was associated with increasing levels of positive, negative and disorganised schizotypal traits in an autistic population, but was unrelated to autistic traits.   Somewhat similarly, Solomon et al (2008) found that response inhibition correlated with formal thought disorder in adolescents with ASD.

A limited number of studies have compared aspects of executive function between autism and schizophrenia. Schneider et al (1987) compared children with autism to a matched group with schizophrenia and found that those with schizophrenia made more perseverative responses on the WCST (indicative of set-shifting difficulties, although not limited to this (Kenworthy, Yerys et al. 2008)) compared to controls, with the autism group scoring midway between the two and not significantly different from either alone. Bolte et al (2002) examined the profile on Wechsler IQ scales between a group of 20 adults with autism and a matched group with schizophrenia. Using a multivariate statistical analysis they found that the autism group outperformed the schizophrenia group on the Similarities subscale (said to measure the ability to generate and think in abstract categories) whereas the schizophrenic group outperformed the autism group on the Comprehension subscale (said to measure the ability to assess the underlying significance of daily living situations). Goldstein et al (2002) used cluster analysis of scores on the Wechsler Adult Intelligence Scale – Revised edition subtests (WAIS-R)

along with perseverative errors on the WCST, time scores from the Trail Making Test and the Halstead Category test (a test of abstraction) to define 4 clusters among individuals with schizophrenia which they labelled moderately impaired, high functioning, severely impaired and severe psychomotor. They then compared these clusters to 31 adults with autism and found that they outperformed all of the schizophrenia groups, except the high functioning cluster, on many of the neuropsychological measures, but that their profile closely resembled the high functioning cluster. It should be noted that other than the high functioning cluster the autism group outperformed the schizophrenia groups by at least 10 IQ points, making it impossible to rule out a global cognitive deficit as driving these results.

Summary of neuropsychological studies of executive function

To summarise, studies in schizophrenia spectrum disorders and autism spectrum disorders have shown widespread deficits across multiple domains of executive functions. The few comparative studies have considered schizophrenia and autism and have found little in the way of definitive differences. There has not been any direct comparison of SPD and ASD, although the literature suggests that some differences may be apparent with respect to sustained attention, verbal working memory and possibly inhibition, which may be less affected in ASD, and generativity, which may be less affected (and potentially even enhanced) in SPD.

2.3.2: Functional magnetic resonance imaging of executive dysfunction

The neuropsychological studies reviewed above provide one method of examining executive dysfunction in autism and schizophrenia; another possible method of investigation is functional magnetic resonance imaging (fMRI). fMRI may be particularly informative when considering two clinically or neuropsychologically similar conditions, as it provides a measure of the underlying brain activity associated with task performance.

fMRI of executive function in the schizophrenia spectrum

Hypofrontality has long been noted in schizophrenia (Ingvar and Franzen 1974), with reduced dorsolateral prefrontal cortex (DLPFC) activation seen in a wide range of executive tasks (Minzenberg, Laird et al. 2009). However, recent meta-analyses of executive tasks have also identified areas of increased activation in people with schizophrenia compared to controls in other prefrontal regions such as the left superior frontal gyrus (BA 6 and 9) and left inferior frontal gyrus (BA 46), right medial frontal gyrus (BA 10) and the left anterior cingulate gyrus (BA 32), as well as in posterior brain regions (temporal and parietal regions, the insula and amygdala) suggesting the problem is not as simple as hypofrontality alone (Minzenberg, Laird et al. 2009). The most utilised executive task in schizophrenia is the n-back memory task, which has been studied in numerous different studies. Hypofrontality has been consistently shown with the n-back task although, as with executive tasks more generally, areas of increased activation in the prefrontal lobe have also been reported in individuals with schizophrenia compared to controls (Glahn, Ragland et al. 2005).

There are many fewer studies using fMRI in people with schizotypal personality disorder than there are of schizophrenia and of these only one has considered executive function. Koenigsberg et al (2005) examined spatial working memory in six individuals with SPD and 5 controls and found that, compared to controls, the SPD subjects showed reduced activation in the left ventral prefrontal cortex (BA 44, 45, 47), superior frontal gyrus (BA10), posterior inferior frontal gyrus (BA44) and intraparietal cortex, while the reverse was true (at trend level significance) for the right middle frontal gyrus (BA46) and right prestriate cortex. It should be noted that this was a region of interest study, which considered approximately 80 regions derived from other studies, but did not correct for multiple comparisons, making the significance of the findings somewhat difficult to interpret.

fMRI of executive dysfunction in ASD

Imaging studies in ASD have investigated a number of different domains of executive function including inhibition, sustained attention, switching attention, planning, fluency and working memory (Philip, Dauvermann et al. 2012). The paradigms employed within each domain vary between studies, with many including emotional stimuli or adding additional elements to test cognitive control mechanisms, making comparison between studies difficult. A recent meta-analysis of all executive tasks showed a degree of both hyper- and hypo-frontality with increased activation in the anterior left middle frontal gyrus (BA11) compared to controls, while reduced activation was seen in the right middle frontal gyrus (BA6 and BA9) as well as non-frontal regions (left inferior parietal

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lobule, right posterior cingulate gyrus, left insula and left lentiform nucleus) (Philip, Dauvermann et al. 2012).

The n-back task of working memory has been employed in two studies of people with ASD. Koshino et al (2005) used a verbal n-back task found highly lateralised differences with reduced activation in the ASD group in the left dorsolateral prefrontal cortex, inferior frontal gyrus, precentral sulcus and inferior parietal lobe, and increased activation in the right inferior frontal gyrus, inferior parietal lobe and bilateral temporal regions. The same group conducted a further n-back study using face identity and found only reduced activity in the ASD group in the left inferior prefrontal and right posterior temporal cortex (Koshino, Kana et al. 2008). A number of other studies have reported hypofrontality during working memory in ASD. Luna et al (2002) used a visuospatial working memory paradigm and reported reduced activation of the dorsolateral prefrontal cortex and posterior cingulate bilaterally. Silk et al (Silk, Rinehart et al. 2006) employed a task of mental rotation, which activates both visuo-spatial and working memory regions, in a small number of autistic individuals (seven) compared to controls. They found reduced activity in the ASD group in prefrontal and striatal regions, but not parietal (visuospatial) regions.

fMRI studies comparing the autism and schizophrenia spectrums
As far is the author is aware, no studies to date have compared executive function in autism and schizophrenia or SPD using fMRI.

Summary of fMRI studies of executive function

In summary, therefore fMRI studies of executive function in ASD, schizophrenia and to a much lesser extent SPD show reduced activation of the prefrontal and striatal regions, suggesting that executive dysfunction arises from broadly similar mechanisms between the groups. There is some evidence that all three conditions also show increases in other prefrontal regions and posterior brain regions during executive tasks, but these appear to be more extensive in schizophrenia than in ASD. These increases are commonly interpreted as reflecting compensatory activity in both conditions, (Minzenberg, Laird et al. 2009; Philip, Dauvermann et al. 2012) ; whether the nature of this compensation is efficient and whether it is the same between conditions is unclear. Compensation through the use of visuospatial systems is often suggested to be important in ASD; such claims are not made for schizophrenia although the extensive activations in non-frontal regions during executive tasks in people with schizophrenia do raise this as a possibility. Only one, very small, study has examined brain activity using fMRI during an executive function task in individuals with SPD and no studies to date have compared ASD with either schizophrenia or SPD directly.

2.3.3: Neuropsychological Studies of weak central coherence

Weak central coherence in ASD

Weak central coherence is a term which was invented by Uta Frith to describe the tendency of autistic individuals to be unaffected by context (Frith 1989). The evidence for weak central coherence in ASD comes from a number of studies conducted by Frith and colleagues. Firstly they had shown that, in contrast to typically developing children,

children with autism showed little improvement in recalling meaningful sentences over random strings of words, suggesting that they showed "a lack of sensitivity to the inherent pattern of the input" (Hermelin and O'Connor 1970; Hermelin and Frith 1971). Following this Shah and Frith (1983) showed that children with autism showed superior performance at the embedded figures test, a task which requires the participant to search for a simple figure which is hidden in a more complex figure. They suggested that this superior performance resulted from a combination of enhanced skill at comprehending the elements within the pattern and being "unhindered …by the dominance of the overall meaning." Further evidence for the weak central coherence theory came when Shah and Frith (1993) later went on to address the enhanced performance of individuals with autism on the block design subtest of the Wechsler Intelligence Scales. The standard part of this task involves putting blocks together to make a design which is provided in a picture. Shah and Frith manipulated the task in three ways: they investigated the effect of providing the design in a segmented form (i.e. divided up into its constituent blocks); they also investigated the effect of rotating the designs; finally they investigated the effect of using more complex designs containing diagonal lines relative the design's orientation. The idea was that if the superior performance on the block design task resulted from superior visuospatial ability then individuals with autism would be less affected by rotating the design or by the inclusion of diagonal lines, whereas if the key factor was weak central coherence then they would show less facilitation with the segmented form than would be seen in a control population (because they were not distracted by the gestalt in the unsegmented form). They found that the latter was true, i.e. unlike the controls the autism group showed little facilitation with the segmented

design, whereas both groups found the task more difficult when the designs were rotated or diagonals were included.

The weak central coherence theory has been investigated by many groups since it was first described, using a variety of tasks in several domains. The most popular directly relevant tasks have been visuospatial tasks (e.g. EFT, block design, Navon hierarchical figures), visual illusions, homograph reading and auditory tasks (tone discrimination, same/different melody judgements). Replication has been most robust for impairment in homograph reading (which requires the use of context to inform pronunciation, e.g. "The road wound around the mountain"; "The wound hurt badly") as well as the enhanced ability on the embedded figures task and the block design task, although some studies do report negative findings on these measures (Happé and Frith 2006). Navon figures, which involve a large letter constructed of smaller letters (Navon 1977), have shown inconsistent findings, which is perhaps surprising given that the findings for other visuospatial tasks have been well replicated. However, multiple factors can affect results on this test, which may account for the heterogeneity in the literature (Navon 2003). Tasks involving visual illusions have shown individuals with ASD to be less susceptible to them (Happé and Frith 1996), indicating that they are not distracted by the context, although again this has not been consistent (Ropar and Mitchell 2001). It has been suggested that a lack of susceptibility to visual illusions and enhanced performance on the block design task may be tapping different abilities (Best, Moffat et al. 2008). Importantly, a number of studies have reported enhanced performance in people with ASD on visual and auditory tasks requiring detailed, or local, processing, but without any

clear sign of impairment in global processing (Mottron, Peretz et al. 2000; Mottron, Burack et al. 2003; Wang, Mottron et al. 2007), leading to the proposal that rather than weak central coherence, individuals with ASD show enhanced perceptual abilities for detail, leading to a preference for local processing, but without deficits in global processing abilities. This is known as the enhanced perceptual functioning theory.

As a result of the research findings since its first description, the theory of weak central coherence has been modified in several ways. Firstly, it is no longer thought that weak central coherence also accounts for the social cognitive deficits in autism, they are now thought to co-exist rather than explain each other. There has also been a shift away from regarding weak central coherence as relating to a deficit in global integration, instead a bias towards local over global processing is now suggested. Finally, probably in response to the enhanced perceptual functioning theory, the superior local processing has been given more prominence with the deficit in global processing de-emphasised (Happé and Frith 2006). A full discussion of these modifications is beyond the scope of the current thesis, but it is worth noting that the last of these has been disputed by Happe and Booth (2008) who suggest that both enhanced local and reduced global processing may be important. This stands in contrast to the enhanced perceptual function theory.

It is therefore generally accepted that individuals with ASD show superior performance to controls on tasks which benefit from a local processing advantage, such as the EFT or block design task. Whether this is accompanied by reduced ability to take into account

the global context (weak central coherence) or the ability to simply ignore global context when it is a distractor and focus on the local (enhanced perceptual function) is less clear.

Weak central coherence in the schizophrenia spectrum

Although the term central coherence is not used, studies of global-local processing are common in schizophrenia and are contradictory, with some reporting impairments in global relative to local processing (Ferman, Primeau et al. 1999; Johnson, Lowery et al. 2005; Poirel, Brazo et al. 2010) while others report impairments in local relative to global processing (Carter, Robertson et al. 1996; Granholm, Perry et al. 1999). All of the aforementioned studies using stimuli based upon the principle of Navon figures and so, as mentioned above, differences in specific task design could account for the inconsistencies.

Several studies have employed tests of visuospatial disembedding in schizophrenia similar to the EFT. Longevialle-Henin et al (2005) report no difference between people with schizophrenia and controls using a group administered form of the embedded figures test. However, within the group with schizophrenia they report decreased performance in those who were rated as disorganised. Similarly Loas et al (2004) found a significant negative relationship between EFT score and the degree of negative and disorganised symptomatology in their group of people with schizophrenia. Chey et al (1997) found that individuals with schizophrenia performed similarly on the easier levels of a disembedding task compared to controls, but less well on the more complex tasks. Magaro et al (1971) examined hospital inpatients and found that individuals with

paranoid schizophrenia and poor premorbid adjustment performed less well on the EFT than controls regardless of the chronicity of their illness; in other individuals with schizophrenia (and indeed people with other psychiatric disorders) a longer length of stay was related to worse performance on the EFT, interpreted by the authors as being the result of institutionalisation. Taken together these findings suggest that in forms of schizophrenia characterised by more negative symptoms or chronic impairment, reduced performance on the EFT would be expected, suggesting a global processing bias, due to poorer local processing, enhanced global processing or both.

In relation to studies of schizotypy, children of mothers with psychosis have been found to perform less well on the EFT than those of well mothers, despite having a similar verbal IQ (Gamer, Gallant et al. 1977).   In a study of schizotypal personality disorder Granholm (2002) found that people with SPD were relatively better at processing Navon Figures shapes on a global level compared to a local level, a finding which was not seen in controls. This is consistent with the same groups work in schizophrenia and suggests a global processing advantage in SPD compared to controls, although the lack of a global processing advantage in their controls is unusual and contrary to much of the literature (Navon 1977).   Contrary to Granholm et al, Parnas et al (2001) found reduced susceptibility to visual illusions in individuals considered to be prodromal for schizophrenia compared to controls who in turn performed better than those with chronic schizophrenia – a finding which indicates a local processing advantage reminiscent of that seen in people with ASD and interestingly suggests that schizotypal and schizophrenic individuals may show a dissociation in performance on these tasks.

However, they also found that both the premorbid and schizophrenic individuals scored less well than the controls on the Navon figures, but do not report whether this reflects a local or global processing bias.

The evidence in schizophrenia and SPD is therefore mixed with no clear indication of whether they are associated with a relative advantage of local to global processing or the opposite. There is some relatively weak evidence that findings in schizophrenia may not be the same as those seen in schizotypal individuals.

Studies comparing the autism and schizophrenia spectrums

A number of studies have compared individuals with autism and schizophrenia using tasks associated with central coherence. Bolte et al (2007) used the EFT, visual illusions, Navon figures and block design task to compare individuals with autism to those with schizophrenia. They found that individuals with high functioning autism outperformed individuals with schizophrenia, but not the typical controls on the EFT. They also found that both high functioning autism and schizophrenia led to reduced susceptibility to visual illusions compared to the controls, which is in agreement with Best et al (2008) that the EFT and visual illusions tests tap different cognitive domains. No differences were seen using the Navon figures or in the block design task. Bolte et al (2007) also conducted a number of tasks to test gestalt principles and found that participants with autism perceived gestalt stimuli less than either those with schizophrenia or controls, suggesting that global processing is impaired in the ASD group but intact in schizophrenia.

In a study which may be relevant to the investigation of schizotypy, Bolte et al (2006) compared parents of children with autism to parents of children with schizophrenia and parents of children with intellectual disability and found that the first group outperformed the other two with respect to the EFT. In keeping with this, Russell-Smith et al (2010) compared students who scored highly on a measure of positive schizotypy (the O-LIFE unusual experience subscale) to a group with a low score on this measure and found that the high scoring group performed worse on the EFT. They also compared a group who scored highly on the AQ to one who scored less well and found that the high scoring group performed better on the EFT. Although they did not compare them directly the scores on the EFT in their high schizotypy group and high AQ group appear to be quite different. The authors interpret their study as supportive of the idea that autism and schizophrenia are diametrically opposed disorders (Crespi and Badcock 2008).

Summary of neuropsychological studies of weak central coherence

To summarise, there is strong evidence that ASD is associated with a preference for local over global processing, although whether this relates to enhanced local processing, impaired global processing or a combination of the two remains unclear. The evidence in schizophrenia and SPD is less clear, but there is some evidence that the opposite may be true. The contradictory nature of the findings may in part relate to the choice of tests employed, which often fail to dissociate local and global processing abilities (Happé and Booth 2008) and are sensitive to slight changes in methodology (Navon 2003).

2.3.4: fMRI of weak central coherence

fMRI of weak central coherence in ASD

A number of studies have examined the brain activation associated with the embedded figures task in autism. Ring et al (1999) compared activation observed during the solving of the EFT against that seen during fixation on a blank screen. They found that the ASD group showed less activation than the controls in the parietal regions (left precuneus, right superior parietal lobule and right supramarginal gyrus), the right inferior and middle frontal gyri and the bilateral occipital cortex. Increased activation was seen in the ASD group in the right occipital cortex, fusiform gyrus and middle temporal gyrus. The authors suggested that these findings indicate that the ASD group use a strategy based less upon working memory and more upon the use of localised visual imagery. Manjaly et al (2007) and Lee et al (2007) used more sophisticated designs where they compared activation during embedded figures performance against that elicited by similar tasks using complex figures without a visual search component. Although both studies report qualitative differences between the groups, no significant differences were seen. Manjaly et al (2007) reported no evidence of prefrontal differences but that the ASD group activated more primary visual areas, suggesting enhanced local processing; Lee et al (2007) reported less prefrontal activations and greater posterior brain activations, similar to Ring et al (1999). Damarla et al (2010) used a design similar to Ring et al (1999) and report similar findings: reduced prefrontal and inferior parietal activation and increased right occipital and bilateral superior parietal activations in the ASD group compared to controls (although a relatively lenient statistical threshold was employed). They also

report reduced frontal-posterior functional connectivity. In contrast to the above studies, Spencer et al (2012) used the same task design as Manjaly et al (2007) and report significant findings of increased prefrontal and reduced visual area activation in ASD. All of the above studies are interesting in that they are indicative of a role of frontal executive functions in solving the embedded figures task. The reductions in prefrontal activations seen in individuals with ASD, may therefore represent executive dysfunction, compensated for by visuospatial systems. Alternatively, they could represent a reduction in the influence of top-down processing (which may normally bias towards global strategies) leading to an increase in bottom-up processing of perceptual information or vice versa. The reductions in front-posterior connectivity reported by Damarla et al (2010) would be consistent with this idea.

Liu et al (2011) argue that the embedded figure designs described above either do not use a suitable control task (Ring, Baron-Cohen et al. 1999; Damarla, Keller et al. 2010) or do not distinguish between global interference impacting disembedding and global processing of a complex shape (Lee, Foss-Feig et al. 2007; Manjaly, Bruning et al. 2007; Spencer, Holt et al. 2012). They therefore compared activation between two different tasks: the first asked individuals to count lines on either possible or impossible 3D objects (a local processing task with interference from automatic global processing), the second asked people to make a judgement of whether a 3D shape was possible or impossible in reality (asserted to be a global processing task). They used a region-of-interest analysis and found that compared to controls the ASD group showed less activation in the counting task relative to the possible-impossible task in the medial frontal cortex.

Functional connectivity of the medial frontal cortex to posterior brain regions was also reduced in the ASD group in the counting versus possible-impossible task. The authors interpret these results as reflecting a decreased distraction by the global form of the object in the counting task in individuals with ASD (evidenced by reduced activation in the medial prefrontal cortex), either due to local bias or enhanced perceptual functioning, but not due to poorer global processing (because performance on the possible-impossible task did not differ).

In the only fMRI study of the block design test to date, Bolte et al (2008) found reduced activation in the visual association area, V2, in individuals with autism compared to controls. Although there is a reduction in activation in a visual region, the authors suggest that it actually may be caused by reduced top-down processing, and hence is reflective of greater bottom up processing of visual stimuli in ASD. However, as the authors' acknowledge there are other possible reasons why reduced activation in V2 may occur in ASD, such as a reduction in effortful processing.

Overall, there is some evidence that fMRI studies have found that individuals with ASD tend to show reduced prefrontal activations and increased activation in visuo-spatial regions during tasks thought to probe central coherence or local-global processing. However, to date the studies do not provide any compelling evidence as to whether this results from enhanced perceptual functioning or from weak central coherence / a lack of top-down processing.

fMRI of weak central coherence in the schizophrenia spectrum

There has been much less fMRI investigation of local-global processing in schizophrenia than in autism. Silverstein et al (2010) used a paradigm which involved attending to a target stimulus when it either stands separately from a group of distractors (isolated condition) or when it is among a group of distractors with a distractor standing separately (embedded condition). They do not report whether there is a significant group x condition interaction, however for the embedded condition they report that compared to controls there is reduced activation in people with schizophrenia in the amygdala, ventrolateral prefrontal cortex, basal ganglia, anterior cingulate and parahippocampal gyrus (all bilateral); increased activation was reported in the left middle frontal gyrus, left ventrolateral prefrontal cortex, left superior parietal lobe, left inferior temporal gyrus and cerebellum. The authors suggest that the increases in activation in the parietal lobe and inferior temporal gyrus is evidence of greater 'bottom up' processing in schizophrenia, i.e. suggestive of a local processing strategy. How this might accord with the increased frontal activations they also report is unclear.

No known fMRI studies have considered SPD or schizotypal individuals in tasks of central coherence or local-global processing.

fMRI studies comparing the autism and schizophrenia spectrums

To the author's knowledge no studies to date have compared weak central coherence / local-global processing in autism and schizophrenia or SPD using fMRI.

Summary of fMRI studies of weak central coherence

Overall therefore fMRI studies are consistent with the idea that individuals with ASD show a relative bias towards local rather than global processing, evidenced by reductions in prefrontal activation. However, it remains unclear whether this bias is the result of enhanced local processing leading to a reduction in global distraction, impaired global processing meaning that they are less able to perceive the whole, both or neither. At present, there are not enough studies to allow one to comment reliably upon the fMRI investigation of local versus global processing biases in schizophrenia or SPD, or to suggest how they may differ or otherwise from ASD. Similar to the behavioural literature there is a need for fMRI studies in both conditions to use stimuli which convincingly isolate local and global processing from each other. Studies of functional and effective connectivity may be useful to further investigate the possibility that reductions in the influence of top-down processing may be important in driving existing findings (Frith 2003).

2.3.5: Social cognition

Social cognition is a broad based concept summarised by Moskowitz as "the study of mental processes involved in perceiving, attending to, remembering, thinking about, and making sense of the people in our social world" (Moskowitz 2005). It therefore represents a vast field of research, covering many facets of human behaviour. Of particular interest in autism and schizophrenia are those aspects of social cognition which involve understanding and interpreting others emotions, intentions and thoughts. Studies

have generally examined these areas in autism and schizophrenia under three related paradigms: emotion recognition, theory of mind and mirror neuron functioning.

2.3.5.1: Neuropsychological Studies of Emotion Recognition

Emotion recognition in ASD

A multitude of studies have investigated the ability of people with autism to recognise basic emotions from faces. The results have been heterogeneous, which may relate to population, task and measurement differences between studies, although overall there does appear to be a deficit in face emotion recognition in people with ASD compared to controls, particularly when more complex stimuli are used, including dynamic and partial expressions (Harms, Martin et al. 2010). The ability to accurately determine emotion from other stimuli, such as voices and gestures, has been less investigated but also appears to be disturbed in people with ASD, suggesting that the deficits are not specific to faces or even the visual domain (Philip, Whalley et al. 2010). The difficulty in recognising basic emotions in ASD is not limited to any particular emotion, although the most commonly reported deficits are in negative emotions such as anger, sadness, fear and disgust (Harms, Martin et al. 2010).

It has been suggested that individuals with ASD use a less efficient method of processing emotional stimuli, specifically local feature based processing as opposed to the more global and automatic strategy employed by typically developing individuals. In support of this, individuals with ASD have been found to perform equally as well at detecting

emotions whether a face is upright or inverted, whereas typically developing individuals perform less well in the inverted condition (Tantam, Monaghan et al. 1989; Gross 2008). It is possible that for more simple stimuli this method of processing emotion is effective enough, or it can be compensated for by other explicit cognitive methods, to allow task performance to be at the level of typical individuals, whereas for more complex stimuli these techniques are insufficient. However, individuals with autism show difficulties in processing facial emotion over and above non-emotional deficits (Philip, Whalley et al. 2010) implying that there is a role for specific dysfunction of the modulating effects of emotion.

Emotion recognition in the schizophrenia spectrum

In schizophrenia, there have also been consistent reports of difficulties in recognising emotions from facial expressions (Marwick and Hall 2008). Again, fewer studies have considered vocal or gestural emotion recognition, but deficits have been reported (Kucharska-Pietura, David et al. 2005; Van den Stock, de Jong et al. 2011). Similar to ASD, impairments are usually, but not exclusively, identified for the recognition of negative emotions (Marwick and Hall 2008). Although there is some debate about whether the deficits are emotion specific or reflective of more general impairment (Johnston, Katsikitis et al. 2001), it is increasingly accepted that the former is the case (Morris, Weickert et al. 2009). In contrast to ASD, the inversion effect in schizophrenia has been reported to be no different from controls (Butler, Tambini et al. 2008).

Studies in schizotypal personality disorder have also examined whether the ability to determine basic emotions from faces is impaired, with conflicting results. Dickey et al (2011) found that individuals with SPD were more impaired in recognising basic emotions than controls using pictures derived from the Ekman faces task. However, when errors on a gender recognition task were taken into account this difference lessened and became non-significant suggesting that the difficulties the SPD group had in emotion recognition were at least in part accounted for by more general difficulties in face processing. Waldeck et al (2000) used a different stimulus set which again employed photographs of people expressing basic emotions and found no significant difference in the ability to identify facial emotion between a group with SPD and typical controls. Mikhailova et al (1996) found that people with SPD were significantly impaired in their recognition of happy facial expressions and there was a tendency towards impairment in their recognition of sad facial expressions. The stimuli used in this study were cartoon pictures of happy and sad faces, as opposed to photographs of real people. One study has examined the detection of emotion from voices in people with SPD in the context of an fMRI experiment and found no differences between the groups (Dickey, Morocz et al. 2010).

A number of studies have also examined the emotion recognition abilities of people who score highly on measures of schizotypy (but not diagnosed with SPD). In the largest of these studies, Germine et al (2011) examined two large groups of individuals (n = 2322 and n = 1514) recruited via the internet using the SPQ and a test of emotion recognition. In the first group they found that emotion recognition abilities were lower in those who

scored highly on the SPQ whereas gender recognition was not. In the second group they replicated the association between SPQ score and emotion recognition and also found that SPQ score did not relate to face identity discrimination. In contrast to these findings, Poreh et al (1994) in a much smaller sample of college students found that those who scored more highly on measures of schizotypy performed less well on measures of face emotion recognition and general face recognition suggesting that the difficulties relate to face processing rather than emotion processing per se.

Abbott et al (2013) recruited individuals through internet advertising and correlated their scores on the Schizotypal Personality Questionnaire (Raine 1991) with those on a video based measure of emotion recognition (The Awareness of Social Inference test – TASIT). They found that higher levels of schizotypy were associated with reduced ability to recognise emotions. In contrast, using the same stimuli and measure of schizotypal traits, Jahshan and Sergei (2007) found no difference between individuals who scored highly on the SPQ compared to low scorers. Toomey et al (1995), using static stimuli, also reported no difference between college students with high schizotypy scores compared to those with low scores.

In one of the only tests which did not involve facial emotion recognition Shean et al (2007) found in a sample of college students that those who scored more highly on the SPQ subscales 'no close friends' and suspiciousness' performed less well at interpreting emotions from posture, whereas those who score highly on 'unusual perceptual experiences' scored less well at interpreting emotions from vocal tone and inflection.

Studies comparing the autism and schizophrenia spectrums

To the author's knowledge there are no studies which have directly compared emotion processing in individuals with SPD to those with ASD. However, there are a limited number of studies which have compared individuals with schizophrenia to those with ASD and controls. Bolte and Poustka (2003) used Ekman faces and found that people with autism scored less well than controls and people with schizophrenia. They also compared performance on the same task in the first degree relatives of their clinical groups and found no significant differences. Couture et al (2010) compared adults with autism and those with schizophrenia to controls on their ability to determine emotion from several different stimuli – movie stills with faces, movie stills without faces and point light displays of emotional movements. They found that both clinical groups performed less well than the controls on the point light motion display tasks and the movie stills with faces task. No effect of emotion was seen in the former, whereas in the latter there was a group x emotion interaction showing that neither clinical group was impaired at recognising fear, both were impaired at recognising sadness and that the autism group were additionally impaired at recognising anger. They also found that, in the movie stills with no faces tasks, the clinical groups performed less well than the controls at detecting sadness, but the autism group actually outperformed controls with respect to recognising fear. One study has compared autism and schizophrenia with respect to non-visual stimuli; van Lancker et al (1989) found that children with autism performed less well than controls on a task of emotion recognition from voices, whereas those with schizophrenia did not differ from controls.

Summary

Overall, therefore there is good evidence that the recognition of basic emotional expressions is impaired in autism and in schizophrenia. The evidence primarily comes from studies of facial expressions, although other sensory modalities have also been investigated and impairments have been seen in both disorders. There is some evidence that emotion recognition is more impaired in autism than in schizophrenia. Although people with both conditions have been found to have difficulty processing face stimuli, regardless of their emotional content, this does not appear to account for the deficits in emotion recognition abilities. It has been suggested that people with ASD have a tendency to process emotional expressions using a local feature based method, rather than a more global inherent emotional method. In schizophrenia, no such local method is suspected, suggesting that the deficits may be associated with a different underlying mechanism. It is possible that the mechanism differ entirely between disorders; alternatively the mechanism may be the same but differ in its severity, such that no compensatory local strategy is required in schizophrenia because the primary deficit is less marked than in autism; or there may be some commonalities and some differences between the disorders, for example, in both conditions there may be aberrant emotional circuitry but with additional impairments to global processing in autism. Studies in SPD and schizotypy in the general population are less clear as to whether impairments in emotion recognition exist and there is marked heterogeneity in the results.

2.3.5.2: fMRI studies of emotion recognition

In typically developing individuals the recognition of basic emotions is thought to involve the interaction of sensory and limbic regions with the prefrontal cortex (Diwadkar, Wadehra et al. 2012). Facial expressions have been some of the most studied communicants of emotion and it has been proposed that there exists a core area for face perception comprising three regions (Haxby, Hoffman et al. 2000). In this model, the inferior occipital gyri are involved in early perception of facial features, the fusiform gyrus processes invariant features of faces which allow people to detect identity, and the superior temporal sulcus is involved in dynamic aspects of facial expression which allow one to detect emotion. Input to the superior temporal sulcus from limbic regions is then implicated in the recognition of emotions, although limbic regions are also active during the processing of neutral facial expressions (Fusar-Poli, Placentino et al. 2009). Specific emotions have been associated with specific limbic regions: for example, the insula has commonly been found to be activated during tasks which involve disgust and anger, while the amygdala is associated with the recognition of fear, happiness and sadness (Fusar-Poli, Placentino et al. 2009). These regions are also known to be activated during the sensation of emotion, a finding which has been suggested as evidence that they form part of a mirror neuron network (see Chapter 2.3.5.5).

Others have argued that such a clear dissociation (i.e. specific regions for invariant versus dynamic components of faces) is not clearly upheld by the evidence and that both the fusiform gyrus and the superior temporal sulcus are involved in emotion processing (Calder and Young 2005).

fMRI of emotional recognition in ASD

Initial studies in ASD reported reduced activation of the fusiform gyrus during face processing paradigms (Pierce, Müller et al. 2001) and this has been confirmed by a meta-analysis which reported that individuals with ASD show reduced left fusiform and right inferior occipital gyrus activations, as well as increased bilateral superior temporal gyrus activations during basic social tasks (mainly face processing tasks, some with emotional content) (Philip, Dauvermann et al. 2012). However, the role of eye gaze has been suggested to be important with some studies reporting a positive relationship between fusiform gyrus activation and time spent looking at the eyes (Dalton, Nacewicz et al. 2005) and others finding no differences in fusiform gyrus activation if individuals are directed to look at the eyes (Hadjikhani, Joseph et al. 2004; Hadjikhani, Joseph et al. 2007).

Amygdala dysfunction has been proposed as a potential mechanism to explain autism (Baron-Cohen, Ring et al. 2000) and fMRI studies of face processing have reported a mixture of hypo (Ashwin, Baron-Cohen et al. 2007; Pelphrey, Morris et al. 2007; Grèzes, Wicker et al. 2009) and hyper-activation (Dalton, Nacewicz et al. 2005). Dalton et al (2005) reported that in people with ASD amygdala activation correlated with the length of time they spent looking at the eyes of neutral stimuli, suggesting that there was an anxiogenic effect of direct eye gaze which was not seen in controls. An alternative explanation for increased amygdala activation was proposed by Kleinhans et al (2009) who found that, in contrast to controls, individuals with ASD did not show habituation

over time of the amygdala response to neutral faces leading to a relative, but not an absolute hyperactivation.

fMRI of emotion recognition in the schizophrenia spectrum

Studies in schizophrenia have also implicated dysfunction of the fusiform gyrus and amygdala during face processing with hypo-activation of these regions being most commonly reported (Phillips, Williams et al. 1999; Takahashi, Koeda et al. 2004; Williams, Das et al. 2004). A recent meta-analysis confirmed these findings, with areas of reduced activation during facial emotion processing being reported in people with schizophrenia compared to controls in the fusiform gyrus, parahippocampal gyrus, amygdala, lentiform nucleus and the superior frontal gyrus (Fusar-Poli, Placentino et al. 2009). Interestingly, it has been proposed that hypoactivation of the amygdala seen in people with schizophrenia when viewing fearful faces is in fact a function of hyperactivation when viewing neutral faces, i.e. activation of the amygdala in people with schizophrenia is not actually less than in controls but the relative increase in activation between the neutral and fearful faces conditions is greater in controls (Hall, Whalley et al. 2008). In contrast to the finding of Kleinhans et al (2009) in autism, this study also reported that there was no difference in the habituation of the amygdala response over time between people with schizophrenia and controls.

There has been only one fMRI study which has considered emotion recognition in individuals with SPD. Dickey et al (2010) examined emotional prosody recognition during the reading of sentences with emotionally neutral meanings. Both groups

activated the superior temporal gyrus regardless of whether the sentences were read in a neutral or emotional tone, with no significant differences found between the groups. An exploratory analysis, using a liberal statistical threshold of $p<0.001$ uncorrected for multiple comparisons, found that individuals with SPD had large haemodynamic responses in frontal regions which were not seen in controls.

A number of studies have considered the brain activation associated with emotion recognition in schizotypal traits in general population samples. Germine et al (2011) examined the effect of social anhedonia, a personality trait known to be associated with schizophrenia (and autism), on brain activation during the viewing of emotional faces. They found that high levels of social anhedonia were associated with both increased and reduced activations in a variety of brain regions using an uncorrected threshold of $p<0.001$ uncorrected. They then used small volume corrections for certain social brain regions, and report that individuals with high social anhedonia showed significantly reduced activation ($p<0.05$ corrected) in the medial frontal cortex, postcentral gyrus and right superior temporal gyrus, compared to those with low social anhedonia.

Huang et al (2013) compared brain activation during the viewing of dynamic facial expressions of happiness appearing and disappearing. They found that during the viewing of happiness disappearing, individuals with schizotypal traits deactivated less in the right anterior cingulate cortex than those with low levels of schizotypal traits.

Studies comparing the autism and schizophrenia spectrums

No studies have directly compared emotion processing in autism and schizophrenia. However, a recent activation likelihood estimation (ALE) meta-analysis compared brain activation during facial emotion processing tasks between studies of people with autism to those with schizophrenia. They found that an increase in activation in people with ASD compared to those with schizophrenia in the superior temporal gyrus and anterior cingulate bilaterally and the left posterior cingulate. In the reverse contrast (schizophrenia > ASD) they found differences in the left inferior frontal gyrus, left parahippocampus, left inferior parietal lobe, right inferior occipital lobe and the cerebellum (Sugranyes, Kyriakopoulos et al. 2011).

Summary

Overall, the functional MRI data in both autism and schizophrenia clearly indicate abnormal activation during the processing of emotions, particularly from faces. However, there is a great deal of heterogeneity between studies, with regard to whether affected individuals under- or over-activate particular areas. This is particularly the case in studies of autism, those of schizophrenia tend to report hypoactivation of social brain regions during emotional processing. Reduced activation in the fusiform gyri is consistently reported in both conditions which may reflect the processing of facial stimuli in areas outwith those typically associated with face processing. This is consistent with the idea that individuals with autism, and possibly also schizophrenia, have not developed regional specialisation for face processing in the same way as unaffected individuals (although whether this is cause or effect is not addressed by these studies). Abnormal

activations in limbic regions have been reported in both ASD and schizophrenia during emotion processing, with both hypo- and hyper-activation reported in the former and mainly hypo-activation in the latter. However, there are some suggestions that these findings may relate to other factors, such as hyper-activation during the viewing of neutral faces in schizophrenia and a lack of the typical habitation of the amygdala in ASD. Increased activation of the superior temporal sulcus during emotion processing has found in people with autism and not those with schizophrenia suggesting that this is an area of potential difference between the groups, and this was highlighted in the meta-analysis by Sugranyes et al (2011). This meta-analysis also suggested that people with schizophrenia show greater activation than those with autism in the inferior parietal lobe and inferior frontal gyrus (potential mirror neuron regions – see Chapter 2.3.5.5). It is not clear from the few existing studies whether individuals with SPD show consistent differences in activation from controls during emotion processing.

2.3.5.3: Neuropsychological studies of mentalising

Mentalising, or theory of mind, describes the ability of individuals to attribute mental states to others and to themselves (Premack and Woodruff 1978; Frith 2003). Studies in typically developing children have shown that most develop this ability from around the age of two (Leslie 1987).

Mentalising in ASD

Baron-Cohen et al (1985) in a now classic paper showed that 80% of autistic children, aged 4, failed a false belief test which was passed by 85% of typically developing

children and 86% of children with Down syndrome (whose IQ was actually lower than the autistic children). The false belief test they employed was the Sally-Anne test, illustrated in Figure 2.1.
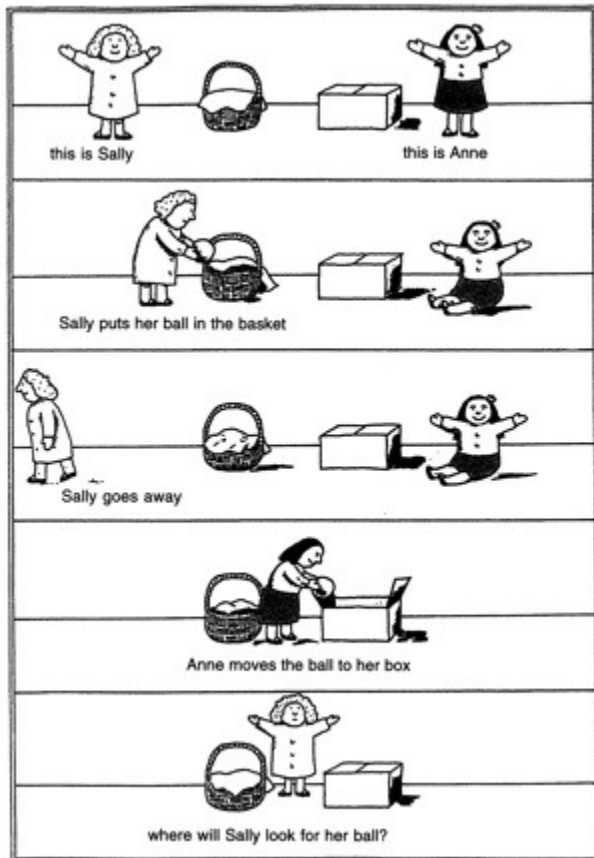
Figure 2.1: Sally-Anne test from (Frith 2001). Participants who fail to answer the question correctly are deemed to be unable to attribute a mental state to Sally that is different from their own. This is a first order false belief tests, i.e. it involves the construct "I think that she thinks"

The work of Baron-Cohen and colleagues has been replicated many times by many different research groups in many different ways. Individuals with autism have, among other things, been shown to be impaired in tasks which involve understanding second order false beliefs (I think that she thinks that he thinks) (Holroyd and Baron-Cohen

1993), detecting faux pas (Baron-Cohen, O'Riordan et al. 1999), determining people's mental states from pictures of their eyes (Baron-Cohen, Wheelwright et al. 2001) or tone of voice (Rutherford, Baron-Cohen et al. 2002), making social judgements from pictures of people (Philip, Dauvermann et al. 2012), understanding irony (Happé 1994) and many more functions. However, not all individuals with autism fail on tasks which purport to test mentalising abilities suggesting that impaired mentalisation is not an invariant feature of autism, the tasks used are solvable by means other than the use of a specific mentalising system, or the tasks used do not capture the actual deficit. Some have proposed that failure to pass false belief tasks is actually the result of executive dysfunction, as these tasks require the use of working memory (to hold the false representation in mind) and inhibition (of the tendency to answer based on what you, as opposed to 'Sally' know to be true) (Tager-Flusberg 2007). In addition, it is now proposed that a delay in acquiring mentalising abilities, rather than a permanent deficit, is what is actually associated with autism (Happé 1995). However, adults with Asperger syndrome have also been found to fail more complex tasks of mentalising abilities such as irony detection (Jolliffe and Baron-Cohen 1999), inferring mental states from pictures of eyes (Baron-Cohen, Wheelwright et al. 2001) and making social judgments from pictures (Philip, Whalley et al. 2010). They also show different anticipatory gaze patterns compared to controls on an implicit false belief task despite passing standard explicit false-belief (Senju 2012). This difference in implicit versus explicit mentalising may help to explain why some individuals with autism pass traditional mentalising tasks, which tend to be explicit in nature, but still show clear social difficulties in real life situations, where implicit mentalising is likely to play a prominent role.

Mentalising in the schizophrenia spectrum

That idea that schizophrenia could be associated with aberrant mentalising abilities developed in part out of observations of the similarities between schizophrenia and autism (Frith and Frith 1991; Frith 1992). Given the clinical overlap between the negative symptoms of schizophrenia and autistic traits, it is not surprising that the most severe mentalising difficulties are found in patients with negative and disorganised symptoms in particular (Sprong, Schothorst et al. 2007). However, deficits in mentalising are also found in individuals with paranoid symptoms and it has also been proposed that certain types of delusion are associated with over-mentalising (i.e. the over-ascription of mental states to others leading to the selection of an incorrect one) (Abu-Akel and Bailey 2000; Frith 2004). Hallucinations and passivity phenomena have also been ascribed to similar problems with self-monitoring (Frith 1992). In keeping with this, the over-ascription of mental states to non-intentional animations has been reported to be associated with patients with schizophrenia and delusions of persecution (Blakemore, Boyer et al. 2003). Frith (2004) has also proposed that there are explicit theory of mind deficits in schizophrenia but, in contrast to autism, implicit processing is intact. Although arising after the current study was conceived, the application of the implicit mentalising task from Senju et al (2012), to schizophrenia would therefore be of interest.

To the author's knowledge no studies of mentalising abilities exist in individuals with a diagnosis of schizotypal personality disorder. However, deficits in mentalising in

abilities have been reported in individuals with schizophrenia who are not actively psychotic, suggesting that they are at least in part trait (not just state) related (Sprong, Schothorst et al. 2007). There are also a relatively large number of studies which consider non-clinical samples with high levels of schizotypal traits and of relatives of people with schizophrenia. In general, these show reductions in performance of mentalising tasks compared to people with low levels of schizotypal traits or controls (Langdon and Coltheart 1999; Langdon and Coltheart 2004; Marjoram, Miller et al. 2006; Fyfe, Williams et al. 2008; Gooding, Johnson et al. 2010; Barragan, Laurens et al. 2011; Aldebot Sacks, Weisman de Mamani et al. 2012), although this is not entirely consistent (Jahshan and Sergi 2007; Fernyhough, Jones et al. 2008; McCleery, Divilbiss et al. 2012; Fett and Maat 2013). A recent meta-analysis showed that, compared to controls, first degree relatives of people with schizophrenia were impaired in mentalising tests (Lavoie, Bédard Lacroix et al. 2013).

Some groups have also reported specific patterns of difference in relation to symptoms. Fyfe et al (2008) studied well individuals divided by the level of schizotypal traits (using the Schizotypal Personality Scale) or delusional thinking (measured using the Peters et al Delusions Inventory) using several tasks designed to probe whether schizotypal individuals made more allocations of connectedness between stimuli (apophenia) or attributed mental states to stimuli when there was none. The tasks used were stories based upon Happe's strange stories (Happé 1994), the triangles task (Castelli, Happé et al. 2000) or the contingency task (Blakemore, Boyer et al. 2003). They found that individuals who scored highly on schizotypy or delusion prone individuals were more

likely to perceive connectedness between stimuli and that delusion prone individuals showed evidence of over-mentalisation in the triangles task and the contingency task (similar to the findings of Blakemore et al (2003).) Similarly, Gray et al (2011) found that higher levels of schizotypy were associated with a greater tendency to ascribe mental capacities to objects which would not normally be held to possess these, including trees, dead people, robots and animals.

Pickup (2006) found that positive schizotypal symptoms, measured on the O-LIFE, were negatively associated with performance on a mentalising task, and that this was not affected by executive function or verbal IQ. No relationship between negative or disorganised signs and task performance were seen, suggesting that this relationship is restricted to clinical populations. Similar results have also been reported by Gooding et al (2010) and Barragan et al (2011). Aldebot-Sacks et al (2012) reported associations between reduced mentalising abilities and positive schizotypal traits in a large sample of undergraduates (420 individuals), but the opposite relationship was seen with disorganised traits. In the unaffected relatives of people with schizophrenia derived from the Edinburgh High Risk Study, Marjoram et al (2006) reported reduced performance on a self-monitoring and a visual joke task, but only in those who had experienced subclinical psychotic symptoms.

Studies comparing the autism and schizophrenia spectrums

Despite the clear overlaps there are relatively few studies which have directly compared mentalising abilities between schizophrenia and autism.

Craig et al (2004) examined individuals with Asperger Syndrome and compared them to a group with schizophrenia and persecutory delusions and a group of controls with regard to their performance on a variety of tests hypothesised to relate to persecutory beliefs. The tests included two mentalisation tasks and the Attributional Style Structured Interview (responses on which had previously been found to relate to paranoia). They found that both the schizophrenia and the Asperger groups performed less well than controls on the mentalisation tasks, but only the schizophrenia group showed atttributional abnormalities, which they interpreted to mean that psychotic symptoms in Asperger syndrome arise from a different mechanism than in schizophrenia.

Couture et al (2010) compared a group of individuals with schizophrenia, a group with high-functioning autism and a group of controls on a battery of social cognition tasks, including emotion recognition, a task of making trustworthiness judgements from pictures and the making social judgements from pictures of eyes. They found that the schizophrenia and autism groups performed less well on aspects of emotion recognition and on rating trustworthiness. In the latter both the autism and the schizophrenia group rated the untrustworthy faces more positively than the controls. When the schizophrenia group was divided into those with positive symptoms and those with negative symptoms, the negative symptom group showed most resemblance to the autism group. Interestingly, the positive symptom group rated the trustworthy faces less positively than the negative symptom or autism group. These findings are consistent with the idea above that the negative symptoms of schizophrenia are associated with a different form of

mentalising difficulty than the positive symptoms, and it is the former which is more like similar to that found in autism.

Pilowsky et al (2000) used a deception task and a false belief task and found that children with autism performed less well than controls on both tasks and less well than children with schizophrenia on the deception task. Children with schizophrenia performed less well than controls on the false belief task but not the deception task, suggesting that they possess similar but less severe mentalising difficulties than children with autism.

Summary

Overall therefore there is evidence that individuals with schizophrenia, SPD and autism all show impairments in mentalising abilities. There is some suggestion in the literature that the nature of the mentalising difficulties may differ between the groups and depend upon the symptoms expressed, with over-mentalising occurring in schizophrenia spectrum disorders with positive symptoms, and under-mentalising in association with autism and with negative symptoms in schizophrenia spectrum disorders.

2.3.5.4: fMRI studies of mentalising

Given that attributing and understanding the mental states of others often involves the detection of emotion, it is unsurprising that mentalising is associated with activation in regions known to be associated with emotional processing, such as the insula, amygdala, and superior temporal sulcus. The amygdala is involved in mediating the conditioned association of a stimulus to an emotional state and is therefore activated, not only when

an emotion is viewed in another, but also when any stimulus is viewed that is associated with a learned emotional characteristic (Frith 2007). As described earlier the superior temporal sulcus, particularly the posterior aspect, is thought to be involved in the processing of dynamic biological stimuli and through this has a role in the recognition of emotional expressions. However, it has also been suggested to have a broader role to play in social cognition, through the evaluation of intentions conveyed through biological motion (Pelphrey, Shultz et al. 2011) and / or through its interaction with the different areas of the social brain with which is co-activated (Hein and Knight 2008).

Other brain regions have also been found to be activated during mentalising tasks, including the medial prefrontal cortex, inferior frontal gyrus, precuneus and temporal poles (Frith 2007; Van Overwalle 2009; Mar 2011). The medial prefrontal cortex has been consistently found to be activated during mentalising tasks, self-processing, action monitoring and outcome monitoring (Amodio and Frith 2006). The anterior rostral aspect has been suggested to be particularly involved in mentalising, possibly through a role in constructing second order representations which underpin certain communicative function (i.e. being aware that the person communicating with us is aware of our mental state) (Frith 2007). It has also been suggested to have a key role in the attribution of enduring social traits to others and their application to day to day situations (Van Overwalle 2009). The temporal poles have also been suggested to be involved in this function through their role in taking pieces of information and weaving them into a whole, thereby facilitating contextual understanding and integrating general social knowledge into specific situations (Mar 2011). The precuneus is richly connected to

other cortical regions and through these connections is thought to be involved in episodic memory retrieval, visuo-spatial imagery and self-processing, the latter due to its association with the medial prefrontal cortex (Cavanna and Trimble 2006). The inferior frontal gyrus has been characterised in animals and humans as a potential mirror neuron region and hence involved in social understanding through a specific mechanism discussed below.

fMRI of mentalising in ASD

Aberrant activations in many of the regions outlined above have been reported in people with ASD during mentalising tasks (Di Martino, Ross et al. 2009; Philip, Dauvermann et al. 2012). The meta-analysis by Philip et al (2012) reported increased activations during complex social cognitive tasks (of which around half were mentalising tasks) in the left superior temporal gyrus, right inferior frontal gyrus and left pre-and post-central gyri, while reduced activations were found in the bilateral superior temporal gyrus and left inferior parietal lobule. Using a much more restricted set of studies, focused purely on mentalising tasks, Sugranyes et al (2011) reported no areas of increased activation in people with ASD compared to typically developing controls; reduced activation was seen in the left medial frontal lobe, right precentral gyrus, left anterior cingulate, left amygdala, left middle temporal gyrus and left inferior parietal lobule.

fMRI of mentalising in the schizophrenia spectrum

Findings in schizophrenia also indicate that mentalising regions are activated differently than in typical controls. In their meta-analysis, Sugraneyes et al (2011) report increases

in activation in the right paracentral lobule and left posterior cingulate; reduced activation was found in the left medial frontal lobe, right posterior cingulate, left middle temporal gyrus and left pulvinar.

There are no studies of SPD which have examined mentalising abilities. However, three studies have examined the relationship between schizotypal traits and brain activation during mentalising tasks using fMRI in general population samples. Using a task of irony detection, Rapp et al (Rapp, Mutschler et al. 2010) found that schizotypal traits as measured by the SPQ correlated negatively with activation in the bilateral middle temporal gyrus and positively with activation in the left inferior prefrontal gyrus. No effect of schizotypal traits was seen on other regions found to be differentially activated during reading ironic and non-ironic sentences. Premkumar et al (2012) compared brain activation in individuals from the general population with high schizotypy to those with low schizotypy (measured by the O-LIFE) when they were viewing scenes of either social acceptance or rejection. They found that high schizotypy individuals showed reduced activation in the anterior cingulate cortex bilaterally, right superior frontal gyrus and left ventral prefrontal cortex when viewing scenes of rejection compared to acceptance. Modinos et al (2010) considered the effect of 'psychosis proneness' in a general population sample on brain activity when participants completed cartoon based first and second-order mentalising tasks. They found that those with high psychosis proneness showed increased activation in prefrontal regions (anterior, dorsomedial and dorsolateral prefrontal cortex).

Mentalising paradigms have also been used in studies of people at risk of psychosis due to either genetic or symptomatic reasons, some of whom may have schizotypal traits. Marjoram et al (2006) found greater activation in the right inferior parietal lobule and bilateral middle frontal gyrus during the viewing of mentalising cartoons compared to physical cartoons in people with a family history of schizophrenia and no history of psychotic symptoms compared to those with a similar family history who had symptoms. No differences between the familial high risk groups and the controls were seen. Brune et al (2011) used a similar cartoon based task and found that individuals with prodromal symptoms of psychosis showed greater activation than both controls and people with schizophrena in the left inferior frontal gyrus, the temporo-parietal junction and left superior and middle temporal gyri. They also showed increased activation compared to controls in the right posterior cingulate and right precuneus. Reduced activation compared to controls was seen in the medial frontal lobe and posterior cingulate gyrus.

Studies of people with schizotypal traits and those at risk of schizophrenia are therefore heterogeneous in terms of their activation patterns during mentalising tasks. Both increases and decreases in brain activation in social brain regions have been found. Differences between the studies in the tasks used and how they define their groups may account for these differences. Unfortunately the degree to which their results can be extrapolated to people with SPD is therefore limited.

Studies comparing the autism and schizophrenia spectrums

One study has directly compared schizophrenia and autism using fMRI during a social cognition task. Pinkham et al (2008) measured brain activation while participants made judgements of trustworthiness from faces. They compared individuals with ASD, a group with schizophrenia and prominent paranoid symptoms and a group with schizophrenia and few paranoid symptoms. Using an ROI analysis and an uncorrected statistical threshold ($p<0.05$), they found that individuals with ASD did not differ from those with paranoid symptoms, but did show less activation in the right amygdala and left ventrolateral prefrontal cortex than the non-paranoid group of people with schizophrenia. The very liberal statistical threshold chose in this study means that it is very difficult to determine whether the results arose from chance alone.

Somewhat more reliably, Sugraneyes et al (2011) also conducted an ALE meta-analysis comparing autism to schizophrenia during mentalising tasks. They report that people with schizophrenia showed greater activation than those with ASD in the right medial frontal lobe, left paracentral lobule and left posterior cingulate. Only one region (the right insula) was found to be more active in ASD compared to schizophrenia. It should be noted that this comparison was based upon combining the data from studies of ASD compared to controls with those of schizophrenia compared to controls and thus may be biased by the use of different paradigms in different clinical groups.

There are no studies to date that directly compare individuals with SPD to those with ASD.

Summary

Overall therefore there is good evidence that individuals with schizophrenia and those with ASD show aberrant brain activation during mentalising tasks in brain regions which have been found to be involved in such tasks in controls. Both under- and over-activation have been reported in both groups in regions across the social brain. The most reliable evidence of potential difference between the groups comes from the meta-analysis of Sugraneyes et al (2011) which suggests that, although individuals with schizophrenia and those with ASD both tend to under-activate mentalising associated brain regions compared to controls, when the two groups are compared generally greater activations are found in individuals with schizophrenia. There is some evidence from the existing literature that individuals with schizotypal traits (either in general population samples or in high risk groups) may show increased activation in at least some brain regions compared to controls, although the literature is very heterogenous and does not permit firm conclusions to be drawn. Whether increases and decreases in activation reflect hyper- and hypo-mentalising is not clear.

2.3.5.5: The mirror neuron theory

The mirror neuron theory is derived from the, initially incidental, observation that neurons in the inferior premotor cortex of a macaque monkey known to fire during goal directed movement, such as grasping an object, also fired when it observed the experimenter carrying out similar movements (Di Pellegrino, Fadiga et al. 1992). Similar neuronal behaviour has since been reported in the inferior parietal lobule of monkeys and

it has been observed that these neurons fire differently at the time of the action depending on what the outcome of the action was (for example grasping to bring food to mouth or to place it in a container) (Fogassi, Ferrari et al. 2005). It has therefore been suggested that the role of these so-called mirror neuron regions is to allow observers not just to judge the goal of an observed action but also the intention that lies behind it. Other areas of the macaque parietal lobe have also been suggested to contain mirror neurons – the lateral intraparietal area which is thought to be involved in the mirroring of the observed other's eye gaze and the ventral intraparietal area which is suggested to be involved in the representation of the observed other's peri-personal space (Rizzolatti and Sinigaglia 2010). Connections to parietal regions from other cortical regions such as the superior temporal sulcus and middle temporal gyri are said to provide higher order sensory information which modulates the response of mirror neurons.

Findings from the macaque have been extended to humans using electroencephalography (EEG), transcranial magnetic stimulation (TMS) and fMRI. EEG studies have shown desynchronisation of the mu rhythm during both movement and the observation of movement, with greater suppression occurring during goal directed than non-goal directed movement (Muthukumaraswamy, Johnson et al. 2004). Greater peripheral muscle response to TMS stimulation of the premotor cortex has been shown to be associated with the observation of action, suggested to reflect an increase in cortico-spinal excitability caused by premotor mirror neuron activation (Maeda, Kleiner-Fisman et al. 2002). fMRI studies have shown increased activations in the inferior frontal gyrus and ventral premotor cortex when people observe actions embedded within contexts

which suggested meaningful intentions, compared to actions without context, or actions with incongruous contexts (Kaplan and Iacoboni 2006). Kaplan et al (2006) also found that the increase in inferior prefrontal activation correlated with a behavioural measurement of empathy. Other studies have also shown correlations between measures of empathy and activation of mirror neuron regions during observation of facial expressions (Pfeifer, Iacoboni et al. 2008) and hearing a motor action (Gazzola, Aziz-Zadeh et al. 2006).

As a result of these and other studies it has been suggested that mirror neuron regions play a pivotal role in the ability to understand the actions and intentions of others at a level prior to conscious processing and hence are important in social cognition (Gallese, Keysers et al. 2004; Fabbri-Destro and Rizzolatti 2008; Rizzolatti and Sinigaglia 2010). For motor behaviour, the potential links between imitation and mirror neurons provide one way in which this may be the case (Iacoboni 2009), although it should be noted that macaques do not imitate in the same way as humans (Hickok 2009). However, there is also evidence that mirror neurons in humans occur outwith the regions described in the macaque, suggesting that it is not just the motor system that contains neurons with mirroring properties. Such neurons have also been reported to occur in humans in the medial temporal lobe and medial frontal cortex through single cell electrode recordings in humans with intractable epilepsy who both performed and observed hand grasping and facial expressions (Mukamel, Ekstrom et al. 2010). fMRI studies have also shown insula and anterior cingulate cortex activation both when someone feels disgusted and observes the emotion of disgust in another (Wicker, Keysers et al. 2003; Jabbi, Swart et al. 2007);

similar results have been reported for pain (Singer, Seymour et al. 2004) ; and somatosensory cortex activation has been reported during the observation of touch to another (Keysers, Wicker et al. 2004; Blakemore, Bristow et al. 2005). In a recent meta-analysis, Molenberghs et al (2012) found that activations reported in fMRI studies of action observation and execution identified, not only the 'core' mirror neuron regions but also the insula, temporal gyri, dorsal premotor cortex and cerebellum. When they specifically examined activation patterns for studies of emotional stimuli they found activation in the posterior inferior frontal gyrus, ventral premotor cortex, amygdala, insula and cingulate gyrus. Thus they conclude that neurons with mirroring properties are found in a wide variety of brain regions and become active dependent upon the nature of the task, supporting the idea that they are involved in functions which are not purely motor.

The mirror neuron theory in ASD

Since the discovery of mirror neurons there has been great interest in their possible role in autism spectrum disorder (Perkins, Stokes et al. 2010). A number of studies have used EEG and reported a lack of mu rhythm suppression in people with ASD during action observation compared to baseline (Oberman, Hubbard et al. 2005; Bernier, Dawson et al. 2007; Oberman, Ramachandran et al. 2008), although none have found a significant group by condition interaction (Hamilton 2013). Other studies have not found mu rhythm suppression during action observation in people with ASD (Raymaekers, Wiersema et al. 2009; Fan, Decety et al. 2010; Bernier, Aaronson et al. 2013) leading some to suggest that it is not a characteristic feature of ASD. fMRI studies in people with

autism have also reported contradictory findings in studies which are designed to directly probe mirror neuron regions (Hamilton 2013). Studies of non-emotional conditions in particular have not provided consistent evidence for mirror neuron dysfunction in ASD, with most studies reporting no differences between controls and people with ASD in mirror neuron region activity during the observation of neutral actions (Williams, Waiter et al. 2006; Grèzes, Wicker et al. 2009; Dinstein, Thomas et al. 2010; Marsh and Hamilton 2011).

Studies of emotional stimuli in autism have shown more evidence of differences in mirror neuron activity between groups, through showing differences in activation of the inferior frontal gyrus and / or the inferior parietal lobule during social or emotional tasks (Dapretto, Davies et al. 2005; Grèzes, Wicker et al. 2009; Greimel, Nehrkorn et al. 2012). However, the inferior frontal gyrus has a variety of functions other than acting as a mirror neuron region, including language, working memory and fine movement (Liakakis, Nickel et al. 2011) and it is possible that the differences reported relate to one of these. In addition in meta-analyses of social tasks in ASD, either no difference (Di Martino, Ross et al. 2009) or an increase in inferior frontal gyrus activity has been reported during social tasks (Philip, Dauvermann et al. 2012). Only one study has confirmed that differences in inferior frontal activation are associated with execution or induction of the emotion as well as observation (Bastiaansen, Thioux et al. 2011). They reported no differences in activation between individuals with ASD and controls in the inferior frontal gyrus (BA44) during instructed facial movement to form a disgusted expression and the induction of disgust through stimulation with unpleasant tastes. They also found

reduced activation in participants with ASD compared to controls in the inferior frontal gyrus during the observation of facial expressions, but only in younger participants, and suggest that dysfunction in mirror neurons may resolve over time in people with ASD.

Thus, despite its enthusiastic embrace by many, the evidence for mirror neuron dysfunction in autism is not strong. Abnormalities in the function of classical mirror neuron regions have been reported somewhat more consistently in studies of emotional, but not neutral, stimuli raising two possibilities: mirror neuron dysfunction is specific to emotional processing in ASD; or that there is not mirror neuron dysfunction in ASD and these differences reported relate to other aspects of social cognitive function which may interact with mirror neuron areas, such as their top-down modulation by socio-emotional cues (Philip, Dauvermann et al. 2012; Hamilton 2013)

The mirror neuron theory in the schizophrenia spectrum

Mirror neurons are also potentially of interest in schizophrenia, given the social cognitive deficits which are known to occur. They have been considered to a much lesser degree than in ASD but a recent review suggested that mirror neuron dysfunction was an area of potential overlap between schizophrenia and ASD (King and Lord 2011). McCormick et al (2012) found increased mu rhythm suppression during action observation in a group of people with schizophrenia who were actively psychotic compared to controls. They did not find this difference in people with schizophrenia who were not actively psychotic, suggesting it may be a state, not trait, feature of the condition. They suggest that mirror neuron activity is higher in actively psychotic individuals with schizophrenia, i.e. in the

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opposite direction than that which has been suggested in ASD. However, a study using TMS has reported reductions in mirror neuron activity in schizophrenia (Enticott, Hoy et al. 2008), while another has reported positive correlations between theory of mind measures and mirror neuron activity in schizophrenia (Mehta, Basavaraju et al. 2012). Reduced inferior frontal gyrus activation has been reported in several studies of people with schizophrenia using social and emotional tasks although not with a specific focus on mirroring properties (Russell, Rubia et al. 2000; Dichter, Bellion et al. 2010; de Achával, Villarreal et al. 2012). Thus the literature in schizophrenia is small and contradictory, and the idea that deficits in mirror neuron function may be shared between schizophrenia and autism is premature. There are no studies to date which specifically explore mirror neuron function in individuals with schizotypal personality disorder.

The study by Bastiaansen et al (2011) examining autism, also included as a sub-analysis, a group of individuals with schizophrenia. Although they do not say whether there were any differences in inferior frontal gyrus activation between people with schizophrenia and controls, they do report that there were no differences between the schizophrenia group and the ASD group, and that there was no evidence of a significant effect of age on inferior frontal activation in the people with schizophrenia.

Summary

Overall therefore is some evidence that individuals with autism or schizophrenia show reduced activation during social tasks in the regions of the brain thought to contain mirror neurons. Whether these abnormalities relate to deficits in mirror neuron activity is

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unclear, indeed there remains significant controversy over whether mirror neurons have a role to play in social cognition at all (Gallese, Gernsbacher et al. 2011).

2.4: CONCLUSION

Table 2.1 summarises the clinical, neuropsychological and functional MRI findings reviewed above with regard to ASD and SPD. There is considerable overlap between the conditions across all of the literature reviewed. As it stands, the reviewed literature is most in keeping with an overlapping model of disorder (Carroll and Owen 2009; Craddock and Owen 2010), with similarities and differences apparent between the conditions across all of the reviewed the literature. However, no work to date has actually compared ASD and SPD on these dimensions within the same study. Such a comparison would serve two broad purposes: to establish the degree of overlap or otherwise in the observed clinical features and to determine whether these features arise from the same or different underlying mechanisms between the conditions. Such understanding would not only inform current clinical practice, it would also guide research into the underlying cause of these conditions and could assist in the development of better ways to diagnose and treat people affected by these conditions.

	SPD	ASD	Notes regarding potential mechanisms
Clinical Features			
Positive symptoms	Increased	Slightly increased	Hyper-mentalising in schizophrenia and hypo-mentalising in autism?
Negative symptoms / social impairments	Increased	Increased	Associated with hypo-mentalising in both conditions?
Disorganised symptoms	Increased	Increased	Unknown
Repetitive behaviours	Slightly increased	Increased	Unknown
Executive Function			
Sustained attention	Impaired	Equivocal	Hypofrontality in both conditions with some degree of compensation? Compensatory mechanisms unknown - influence of visuo-spatial systems usually highlighted in ASD but potentially also important in SPD
Verbal working memory	Impaired	Equivocal	
Inhibition	Impaired	Equivocal	
Generativity	Superior	Impaired	
Set shifting	Impaired	Impaired	
Planning	Impaired	Impaired	
Weak central coherence / local-global processing	Unclear	Local bias +/- global weakness	ASD may use visuospatial regions more than frontal regions, unknown in SPD. Reduced top-down processing in both?
Social cognition			
Emotion recognition	Impaired	Impaired	Compensatory local strategy in ASD?
Mentalising	Impaired	Impaired	Hyper versus hypo-mentalising?
Mirror Neuron function	Unknown	Impaired	Unknown

Table 2.1: Summary of findings in clinical and neuropsychological studies in ASD and SPD relative to controls

Chapter 3

Experiment I

A clinical comparison of ASD and SPD

3.1: INTRODUCTION

The studies reviewed in the previous chapter have clearly shown that, although there are obvious differences between the clinical presentation of autism and schizophrenia, there are also overlaps, particularly with regard to negative and disorganised symptomatology and social impairment. More obvious differences are apparent between the conditions with respect to age of onset, positive symptoms and delayed speech. However, the broader spectrum forms of these conditions may not conform, or at least not be detected at the same ages as the core disorders. They also show less marked impairments in these key symptom domains: positive symptoms are markedly attenuated in SPD relative to schizophrenia and delayed speech is not required for a diagnosis of Asperger syndrome, indeed it is a specific exclusion criterion (American Psychiatric Association 2000).

The clinical relationship between ASD and SPD is therefore unclear and indeed it may not be possible to differentiate the two on clinical measures alone. As a first step towards clarifying their relationship, a detailed study of their clinical features was conducted. Standardised diagnostic tools were used to establish the degree of overlap between the diagnoses. Given the spectrum nature of these conditions, continuous measures of their core features were also conducted. Standardised measures of associated psychiatric diagnoses and symptomatology were employed. Finally, for those individuals for which it was possible, a standardised developmental history was acquired from a relative.

It was hypothesised that it would be possible in most cases to assign individuals to either a diagnosis of ASD or SPD, but that some people would meet criteria for both disorders.

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Levels of negative and disorganised symptoms were expected to be equal between the groups, but positive symptoms were hypothesised to be more severe in individuals with SPD. Psychiatric disorders were expected to be high in both groups although it was hypothesised that individuals with ASD would show more obsessive behaviours but be less distressed by them than the SPD group. In those in whom it was possible to acquire a developmental history, greater levels of impairment were expected to be seen in early development in the ASD group than the SPD group, with a lessening of these differences over time due to a deterioration in the SPD group, analogous to that reported for schizophrenia.

3.2 METHODS

3.2.1 Recruitment

General inclusion and exclusion criteria

In order to participate in the study all individuals had to be over the age of 25 by the end of the study period to (in order to minimise the risk of later developing schizophrenia). Both male and female individuals were recruited. Individuals with an IQ of less than 70, a history of brain injury, a lack of speech, a history of substance dependence or a history of schizophreniform disorder, schizophrenia or bipolar affective disorder were excluded from the study.

Written informed consent was collected from all individuals who agreed to take part in the study prior to beginning the assessment process.

Participants with Autism Spectrum Disorders

Individuals with ASD were recruited from two sources: the regional autism spectrum disorder consultancy service (RASDCS) or the One Stop Shop for People with High Functioning Autism or Asperger Syndrome in the Lothians (Number 6).

RASDCS is an NHS service to which the author has provided clinical sessions for the last 3 years. It covers Southeast Scotland (Lothian, Borders, Fife and Forth Valley) and is primarily a diagnostic service for adults with suspected ASD who are of normal global intelligence although some individuals with a learning disability are also seen. The RASDCS team is drawn from a wide range of disciplines including psychiatry, nursing, psychology and speech and language therapy. All referrals to RASDCS are made by individuals working in secondary care, i.e. specialist psychiatric services; direct referrals from primary care are not accepted. Individuals seen by the service are assessed by at least one and sometimes two team members who carry out a face to face interview and a developmental history from an informant where practicable. As the service is a clinical one, as opposed to being research based, it is unusual for standardised interviews or assessments to be used. All assessments are discussed at a monthly multidisciplinary team meeting prior to a diagnosis being allocated.

Number 6 is a support service for adults of normal global intellectual ability who have a diagnosis of ASD. It is a voluntary sector service run by Autism Initiatives, although much of the original funding was provided by NHS Lothian and the relevant local area authorities. Strong links exist between Number 6 and NHS services, such that the majority of individuals who attend Number 6 received their diagnosis through RASDCS. Number 6 provides a wide variety of support for individuals with ASD including recreational activities, advice related to employment or benefits issues and groups aimed at psychoeducation or alleviating distress such as anxiety or anger management.

At both recruitment sites the initial approach was made by a person who knew the individual – at RASDCS this was the team member carrying out the assessment, at Number 6 it was a support worker. The individual was given a brief verbal summary of the study and asked if they would mind being contacted by the author to discuss it in more detail. Provided they gave verbal consent they were then sent a copy of the study information sheet. They were contacted within one to two weeks to discuss the study further and arrange a time to conduct the assessments if they wished to take part.

All included individuals had a clinical diagnosis of ASD and met diagnostic thresholds for the social and communication sections of the Autism Diagnostic Observational Schedule (ADOS (Lord, Risi et al. 2000)). An additional exclusion criterion of a diagnosis of schizotypal personality disorder determined using the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II (First and Gibbon 1997)) was included for this group.

Participants with schizotypal personality disorder

Individuals with SPD were recruited from three sources: participants from the Edinburgh High Risk Study of schizophrenia (EHRS), NHS Lothian clinical psychiatric services; and individuals referred to RASDCS who were diagnosed with SPD rather than ASD.

The EHRS was a large scale prospective study carried out in the University of Edinburgh Division of Psychiatry between 1994 and 2004. Individuals with a family history of schizophrenia were recruited in early adulthood and followed up for 10 years. All of the participants in this study have now passed through the period of maximum risk for the development of schizophrenia therefore it can be asserted with a reasonable degree of confidence that those who have not become unwell to date are unlikely to do so in the future. Schizotypal traits and the presence of psychotic symptoms assessed were assessed in the EHRS using the Structured Interview for Schizotypy (SIS (Kendler, Lieberman et al. 1989)) and the Present State Examination (PSE (Wing, Birley et al. 1967)) respectively. Efforts were made to recontact all those who had the presence of mild impairment in four or more domains of the SIS relevant to the DSM-IV features of schizotypal personality disorder, or those who had shown transient or partial psychotic symptoms which were not of a degree sufficient to make a diagnosis of schizophrenia. Contact details were still current for around half of the SPD group. It was possible to access contact details for many of the remainder through the use of the Community Health Index (CHI) system – a national database of all individuals registered with a General Practitioner (GP) in Scotland. Prior to approaching any of the EHRS

participants, contact was first made with their GP to ensure that there were no health-related or other reasons why they should not be contacted.

In addition to the participants from the EHRS a number of individuals were recruited from NHS Lothian clinical services. The computerised Patient Information Management System (PIMS) was used to identify patients in Lothian with a clinical diagnosis of SPD who were in current contact with NHS services. Contact was then made with their consultants to determine whether they would be suitable for inclusion in the study.

Finally a number of participants were recruited from RASDCS after they were referred for assessment for possible ASD but it transpired that they actually met criteria for SPD.

All participants in the SPD group met DSM-IV criteria for SPD, confirmed using the SCID-II. An additional exclusion criterion of scoring above threshold on both the social and communication sections of the ADOS was employed for this group.

Control participants

Controls were recruited from partners and friends of participants as well as NHS staff and support workers from Number 6. Individuals with a personal history of or a first degree relative with ASD, SPD or a psychotic illness were excluded from the study.

3.2.2: Assessment

Investigation of the clinical features of the three groups consisted of 3 strands: assessment of autistic traits, assessment of schizotypal traits and assessment of psychiatric disorder. Each involved a combination of observer-rated and self-rated standardised instruments

3.2.2.1: Assessment of autistic traits

The observer-rated measure and diagnostic tool used was the Autism Diagnostic Observation Schedule – Generic (ADOS-G); the self-rated tools were the Autism Spectrum Quotient (AQ (Baron-Cohen, Wheelwright et al. 2001)) and the Empathy Quotient (EQ (Baron-Cohen and Wheelwright 2004)).

Autism Diagnostic Observational Schedule - Generic

The ADOS-G is a semi-structured assessment which is widely used as a face-to-face research diagnostic instrument for autism spectrum disorders. It consists of 4 modules, each designed for use with individuals of different age groups and verbal abilities. Module 4 was employed in the current study as it is designed for use with adults with phrase speech.

Practical administration of the ADOS Module 4 involves the use of a combination of free conversation; set questions probing the individuals understanding of social relationships and emotions; and practical tasks such as demonstrating an action, telling a story from a picture book and creating an imaginative story. The aim is to probe specific skills

relevant to the diagnosis of autism and to encourage the participant to interact with the examiner in as natural as possible manner given the situation.

The scoring system for the ADOS is divided into 5 main domains: Communication, Social Interaction, Imagination, Stereotyped Behaviours and Restricted Interests, and Other Abnormal Behaviour.   Other than Imagination, for which only one score is awarded, each of these domains is a composite of different traits which may be associated with autism.   For example, the Communication domain consists of 10 different traits covering areas such as speech abnormalities, quality of conversation and use of gestures. Each trait is awarded a score between 0 and 3, with higher scores meaning that the individual is more severely affected.   Although information is collected on a large number of traits only certain scores from the Communication and Social Interaction domains contribute to the diagnostic algorithm. These are "stereotyped or idiosyncratic use of words or phrases", "conversation", "descriptive, conventional, instrumental or informational gestures" and "emphatic or emotional gestures" from the communication section and "unusual eye contact", "facial expressions directed at others", "empathy / comments on others' emotions", "responsibility", "quality of social overtures", "quality of social response" and "amount of reciprocal social communication" from the Social Interaction section. For the diagnostic algorithm scores of 3 are converted to 2 and a total for each domain generated. A diagnosis of ASD requires a total score of at least 2 for communication, 4 for social interaction and a combined total of not less than 7. A diagnosis of autism requires a total score of at least 3 for communication, 6 for social interaction and a combined total of not less than 10.

The original autism diagnostic observation schedule (ADOS) was published in 1989 and designed for use with children between the ages of 5 and 12 years old (Lord, Rutter et al. 1989). The growing use of the ADOS in clinical practice and the desire for a research tool suitable for other age groups led to the development of the ADOS-G (Lord, Risi et al. 2000). The ADOS-G was validated in a cohort of 223 individuals in total; of these 45 participated in the validity study of Module 4. The gold standard diagnosis for validation was consensus clinical diagnosis which also involved the use of the Autism Diagnostic Interview – Revised (ADI – R (Le Couteur, Lord et al. 2003)). The Module 4 validation study contained sixteen individuals with autism, fourteen individuals with PDD-NOS and fifteen controls who were either typically developing or had one of a range of diagnoses including intellectual disability, receptive-expressive language disorder, attention-deficit hyperactivity disorder, oppositional defiant disorder, anxiety disorder, major depression and obsessive-compulsive disorder. Sensitivity and specificity for the cut-offs described above for module 4 were found to be between 0.76 and 0.93 for all diagnostic discriminations.

Autism Spectrum Quotient

The AQ is a 50 item self-rated instrument designed to measure an individual's autistic traits. Individuals are asked to rate statements such as *"I frequently get so strongly absorbed in one thing that I lose sight of other things"* or *"I find it easy to work out what someone is thinking or feeling just by looking at their face"* using a 4 point scale: definitely agree, slightly agree, slightly disagree or definitely disagree. Responses which

indicate the presence of an autistic trait are given a score of 1 regardless of whether the respondent has indicated definitely or slightly. The AQ yields a total score and a score in 5 different domains: social skill, communication, set switching, attention to detail and imagination. The original validation study found that 80% of people with ASD had a total score of 32 or over, compared to only 2% of the control group (Baron-Cohen, Wheelwright et al. 2001).

Empathy Quotient

The EQ is a 60 item self-rated instrument designed to measure individual differences in empathy. It was developed by the same research group who produced the AQ and follows a similar format. Example statements from the EQ are *"It is hard for me to see why some things upset people so much"* and *"Friends usually talk to me about their problems as they say that I am very understanding"* and are rated using the same 4 point scale as the AQ. Twenty of the questions are 'dummy' questions and are unrelated to empathy so are not scored. Scores of 1 or 2 are awarded to indicate the presence of an empathic trait, thus high scores indicate greater empathy. Around 81% of people with ASD score less than 30 on this scale compared with 12% of controls (Baron-Cohen and Wheelwright 2004).

3.2.2.2: Assessment of schizotypal traits

The observer rated measures were the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II), the Structured Interview for Schizotypy (SIS) and the Positive and Negative Syndrome Scale (PANSS). The SCID-II was used to indicate the presence or

absence of DSM-IV schizotypal personality disorder; the SIS was used to provide a quantitative measure of schizotypal traits; and the PANSS provided a measure of positive and negative psychotic symptoms, as well as general psychiatric symptoms. The Rust Inventory of Schizotypal Cognitions (RISC (Rust 1988)) and the Peters Delusions Inventory (PDI (Peters, Joseph et al. 2004))were the self-rated tools employed.

Structured Clinical Interview for DSM-IV Axis II Disorders

The SCID-II is a well-validated and widely used interview which consists of 119 questions directly mapping to the traits of the 12 DSM-IV personality disorders. Following an affirmative answer examples are sought to clarify the extent to which the trait is present and establish the degree of influence it has on the respondent's life. Each trait is scored on a scale between 1 (absent) and 3 (definitely present). A score of 3 on five of the nine possible traits of SPD are required to make the diagnosis.

Interestingly no data are available on the validity of the DSM-IV SCID-II. A few studies have investigated the validity of the previous version (DSM-III-R SCID-II), although interpretation is difficult due to the lack of uniformly agreed gold standard (First and Gibbon 1997). Skodol et al (1988) compared the SCID-II to a gold standard clinical diagnosis (longitudinal expert evaluation using all data) and found that the diagnostic power (ratio of correct test results to total number of tests administered) of the SCID-II varied between 0.45 (for narcissistic personality disorder) to 0.95 (for antisocial personality disorder). For schizotypal personality disorder the diagnostic power was 0.90.

Structured Interview for Schizotypy (SIS)

The SIS is an observer rated instrument which was developed to examine schizotypal traits in the relatives of individuals with schizophrenia (Kendler, Lieberman et al. 1989). It has been evaluated in several samples of relatives of individuals with schizophrenia, who have scored more highly across a range of the traits it measures. It is divided into 2 sections: the first section takes the form of a structured interview while the second concerns the behaviour observed by the investigator during the interview. Questions in the first section are used to generate summary scores between 1 (marked) and 7 (absent) for a variety of schizotypal traits including several which do not form part of the diagnostic criteria for SPD. The traits scored are social isolation, introversion, sensitivity, social anxiety, ideas of reference, suspiciousness, restricted emotion, magical thinking, illusions, passivity like phenomena, derealisation / depersonalisation, antisocial traits, irritability and impulsivity. The traits rated in the second section are scored between 1 (marked) and 5 (absent) and are rapport, affect, organisation of speech/thought, odd/eccentric behaviour and suspiciousness.

To assist with interpretation in the current study, each item of the SIS was scored and then reflected, such that higher scores represented greater pathology. In addition, in order to limit the number of comparisons the scores were collapsed into symptom dimensions (positive, negative and disorganised). Within the positive dimension were ideas of reference, reported suspiciousness, magical thinking, illusions, passivity like phenomena and observed suspiciousness; negative symptoms included social isolation, introversion,

sensitivity, social anxiety, restricted emotion and poor rapport. Disorganised symptoms included observed affect, organisation of speech / thought and odd / eccentric behaviour.

Positive and Negative Syndrome Scale (PANSS)

The PANSS is a widely used observer rated instrument which provides summary scores for the burden of positive and negative psychotic symptoms as well as containing a scale for general psychopathology (Kay, Fiszbein et al. 1987). It was originally shown to be a reliable and valid measure of symptomatology in a group of 101 individuals with schizophrenia (Kay, Opler et al. 1986). Each item is rated from 1 (absent) to 7 (extreme), with scores of 3 or more considered to be outwith the normal range. There are 7 items contained in the positive symptom domain (delusions, conceptual disorganisation, hallucinations, hyperactivity, grandiosity, suspiciousness/persecution and hostility); 7 items in the negative symptom domain (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, difficulty in abstract thinking, lack of spontaneity and flow of conversation and stereotyped thinking); and 16 items in the general psychopathology scale (somatic concern, anxiety, guilt feelings, tension, mannerisms and posturing, depression, motor retardation, uncooperativeness, unusual thought content, disorientation, poor attention, lack of judgment and insight, disturbance of volition, poor impulse control, preoccupation and active social avoidance).

Rust Inventory of Schizotypal Cognitions (RISC)

The RISC is a self-report questionnaire which was developed to measure schizotypal traits in the general population. It contains 26 items to which the participant chooses one

of four possible response: strongly agree, slightly agree, slightly disagree and definitely disagree. Example statements include *"I consider no person or country to be my enemy"* and *"I would not be in the least bit concerned if a person who believed in magic tried to put a spell on me"*. A score between 0 and 3 is allocated depending on the response with higher scores indicating greater levels of schizotypal traits.

In the original validation study the RISC score was found to be higher in a group with schizophrenia than controls (47.83 vs. 35.67, p=0.001) and to correlate in a general population sample with the psychoticism subscale of the Eysenck Personality Questionnaire (r=0.12) and the emotional instability, non-conformity, low mood and poor social relations subscales of the Minnesota Counselling Inventory (MCI) (r=0.45, r=0.40, r= 0.27 and r=0.26 respectively) (Rust 1988). While this perhaps only represents a partial validation of the RISC, it has since been found to correlate with other psychosis proneness scales (Balogh, Merritt et al. 1991). Moreover, it is associated with the presence of psychotic symptoms in a group of people at enhanced risk of developing schizophrenia due to a family history of the disorder (Miller, Lawrie et al. 2002) and had the highest positive predictive value for later schizophrenia of all the clinical and neuropsychological variables examined in this group (Johnstone, Ebmeier et al. 2005).

Peters Delusions Inventory

The 21 item version of the PDI was used to measure delusional traits in the study participants. This scale was developed for use in the general population and consists of 21 questions covering common delusional beliefs. Example questions from the PDI are

"Do you ever feel as if you are being persecuted in some way?" and *"Do you ever feel as if people seem to drop hints about you or say things with a double meaning?"* If the participant responds positively then they are asked to complete a further three 5 point Likert scales concerning how distressing they find this thought, how much they think about it and how much they believe it to be true. The inventory yields four scores: number of items endorsed, total distress, total preoccupation and total conviction.

The original PDI (Peters, Joseph et al. 1999) was a 40 item questionnaire developed from the Present State Examination. A principal components analysis was used to identify 11 components of the original PDI and the items with the highest loadings for each component were chosen for inclusion in the PDI-21 (Peters, Joseph et al. 2004). The reliability and validity of the PDI-21 was established in a sample of 444 individuals from the general population in whom the scores correlated with other measures of schizotypal traits: the Foulds Delusions-Symptoms-State-Inventory, the unusual experiences subscale of the Oxford-Liverpool Inventory of Feelings and Experiences and the Schizotypal Personality Scale (r=0.61, r= 0.65 and r= 0.51 respectively).

3.2.2.3: Assessment of psychiatric symptoms and disorder

Two tools were administered to assess psychiatric disorder: the Structured Clinical interview for Axis I Disorders (SCID I (First and Gibbon 1997)) and the Florida Obsessive Compulsive Inventory (FOCI (Storch, Bagner et al. 2007)).

Structured Clinical interview for DSM-IV Axis I Disorders: Research Version

The SCID I is structured interview designed to confirm the presence or absence of psychiatric disorder. There are 10 parts to the full SCID I which cover the full range of DSM-IV diagnoses. In the current study three sections were employed: psychotic disorders, affective disorders and anxiety disorders.

As for the SCID-II, validation of the SCID-I is difficult due to the lack of a uniformly agreed gold standard. Several groups have validated earlier versions of the SCID-I against best estimate clinical diagnoses based upon the LEAD standard (longitudinal expert evaluation using all data) where it has been reported to show moderate to good agreement for non-organic psychoses with kappa values of between 0.72 and 0.92 (Fennig, Craig et al. 1994) and to have higher sensitivity and specificity than a routine unstructured clinical interview (Basco, Bostic et al. 2000).

Florida Obsessive Compulsive Inventory

The FOCI is a self-report questionnaire which was developed to provide a quick and reliable method to screen for obsessive-compulsive symptoms. It is divided into two sections: part A and part B. In part A the respondent indicates the presence or absence of 20 common symptoms of obsessive-compulsive disorder. These are divided into 4 sections: obsessive imagery, obsessive ruminations, obsessive impulses and compulsive acts. Should the respondent positively indicate the presence of one or more symptom they are then asked to complete part B to assess the overall degree to which they are affected by their symptoms. Severity is assessed through 5 questions covering the

amount of time occupied by the symptoms, the distress they cause, the degree of (lack of) control over them, any avoidance which occurs as a result of the symptoms and their interference with day to day life. Each of these is rated on a 5 point scale between 0 (none) and 4 (extreme). The FOCI therefore generates two scores: one reflecting the number of symptoms endorsed on the checklist and the other reflecting overall severity. No attempt is made to assess the severity of individual symptoms.

The FOCI was developed by the research group which developed the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) – a widely used clinical interview for the assessment of obsessive compulsive symptoms. It was validated in a population of 113 patients with obsessive-compulsive disorder where the severity score and the symptom checklist score were found to be correlated with the Y-BOCS total severity score (r=0.89 and r=0.47 respectively) (Storch, Bagner et al. 2007).

3.2.3: Statistical analysis

Participant demographic characteristics were compared using Analysis of Variance (ANOVA) and chi squared tests as appropriate. The clinical characteristics were compared using ANOVAs for parametric data and Kruskal-Wallis tests with follow-up Mann-Whitney tests for continuous non-parametric data and chi squared or Fishers exact tests for categorical data. When the latter were used, standardised residuals were inspected to determine where significant differences lay in the contingency table. In order to investigate the effect of global intellectual ability on the results, IQ, as measured by the Wechsler Abbreviated Scale of Intelligence (WASI (Wechsler 1999)) was added

as a covariate to the parametric tests; for the non-parametric data partial correlations between IQ and the characteristic in question were conducted, with group as a covariate. The relationship between autistic and schizotypal traits in each of the groups was examined using parametric and non-parametric correlations as appropriate.
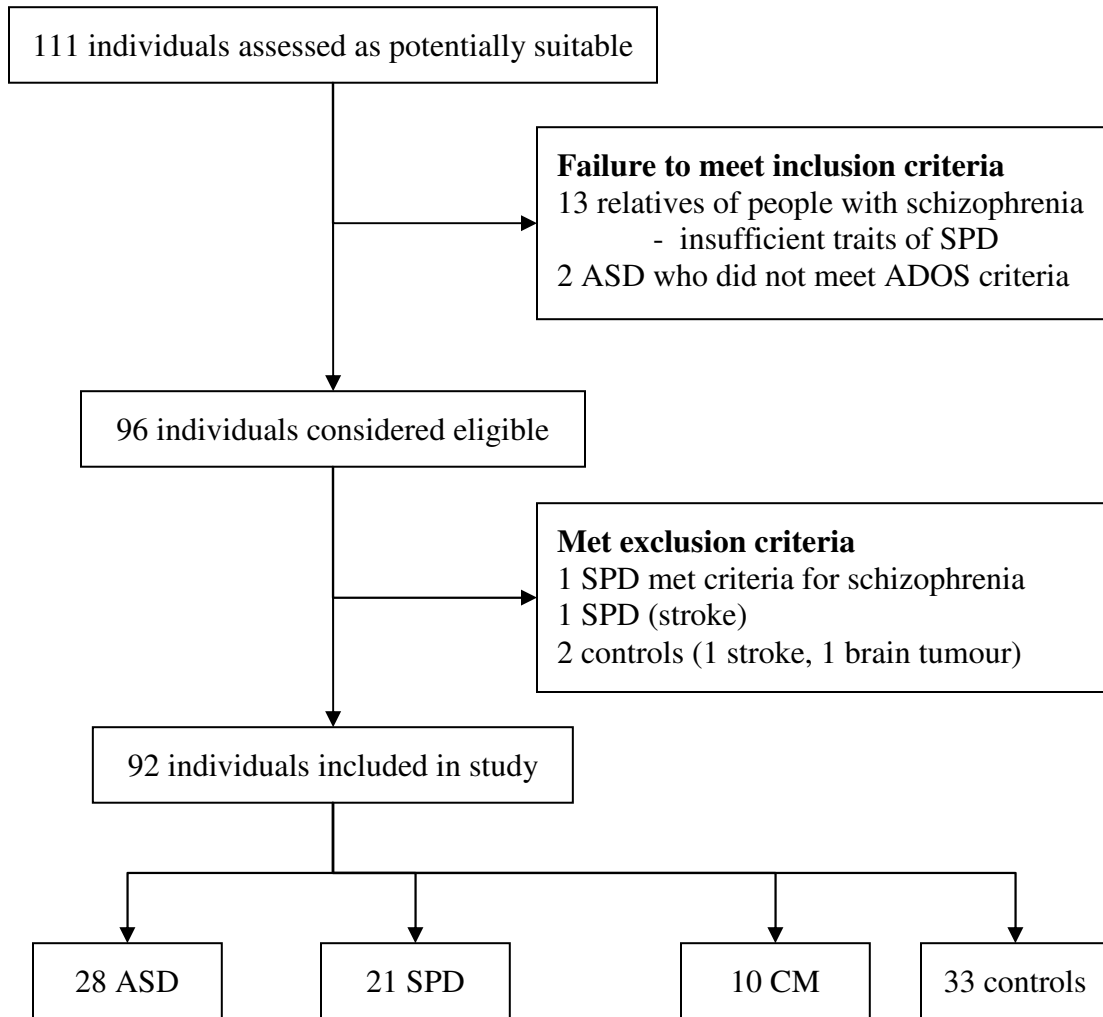
3.4: RESULTS

3.4.1: Recruitment and characteristics of the study groups

Recruitment to the study is summarised in Figure 3.1. A total of 111 individuals were assessed as potentially suitable for the study. Of these, 13 people failed to meet inclusion criteria as, although they were related to people with schizophrenia they had insufficient traits of schizotypal personality disorder. In addition, 2 individual with ASD was not included as they did not meet ADOS criteria. Of the remaining 96 individuals, 2 individuals with SPD were excluded: the first because he also met standardised criteria for schizophrenia and the second because he was found to have suffered a stroke. Two controls were also excluded due to the presence of a brain tumour in one and a stroke in the other.

This left a total of 92 individuals for study: 28 met the inclusion criteria for the ASD group; 21 met inclusion criteria for the SPD group; 10 met the inclusion criteria for both

the ASD and SPD groups and were therefore included in a separate study group, (comorbid group - CM); and 33 were typically developing controls.

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│ 111 individuals assessed as potentially suitable │
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                    │
                    │        ┌──────────────────────────────────────┐
                    │        │ Failure to meet inclusion criteria   │
                    ├───────▶│ 13 relatives of people with schizophrenia │
                    │        │    - insufficient traits of SPD       │
                    │        │ 2 ASD who did not meet ADOS criteria  │
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│ 96 individuals considered eligible │
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                    │        │ Met exclusion criteria               │
                    ├───────▶│ 1 SPD met criteria for schizophrenia │
                    │        │ 1 SPD (stroke)                       │
                    │        │ 2 controls (1 stroke, 1 brain tumour)│
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│ 92 individuals included in study  │
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   │ 28 ASD │ │ 21 SPD │ │ 10 CM  │ │ 33 controls│
   └────────┘ └────────┘ └────────┘ └────────────┘
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Figure 3.1: Flow diagram of recruitment to study

The characteristics of the 4 groups are shown in Table 3.1.

	ASD	SPD	CM	Controls
N	28	21	10	33
M:F	22:6	14:7	7:3	23:10
Age	39.5 (11.6)	37.1 (9.2)	34.9 (9.9)	36.5 (9.3)
Handedness	27:1	19:2	8:2	31:2
Yrs. education	16.2 (1.7)	15.2 (2.0)	16.2 (2.3)	16.5 (1.9)
Verbal IQ	108.4 (14.0)	104.7 (11.9)	98.9 (22.4)	113.2 (9.8)
Performance IQ	114.6 (17.8)	106.7 (11.4)	107.2 (21.3)	119.1 (10.2)
Full-scale IQ	113.1 (17.3)	106.4 (10.7)	103.5 (22.5)	118.1 (9.9)
ADOS comm	3 (2)	1 (2)	2 (1)	0 (0)
ADOS SI	5 (1)	2 (2)	5 (3)	0 (0)
SPD items	2 (2)	5 (1)	5 (2)	0 (0)

Table 3.1: Characteristics of the study groups

M:F – male:female; ADOS comm – ADOS communication score; ADOS SI – ADOS social interaction score; SPD items –items endorsed on SCID-II SPD subscale

No significant differences were seen between the groups with respect to gender (chi sq = 0.99, p= 0.80), handedness (Fishers exact test = 3.07, p=0.33), age (F=0.55, p=0.65) or years spent in education (F=1.29, p =0.28). IQ scores differed significantly between the groups (F=3.59, p=0.02; F=3.65, p=0.02; F=4.12, p=0.009 for verbal, performance and full-scale IQ respectively). The control group had significantly higher IQ scores in all three domains than either the SPD or the CM group (all p<0.05). The ASD, SPD and CM groups did not differ significantly on any of the IQ measures (all p>0.08).

As would be expected, the ASD group scored more highly than the SPD group and the controls on the ADOS communication and social interaction subscales, while the SPD group scored more highly than the ASD group or the controls on the number of endorsed items in the SPD section of the SCID-II. No difference was seen between the CM group and the ASD group on the communication subscale of the ADOS (Z=-1.13, p=0.26); however there was a trend towards a significant difference in the social impairment subscale with the CM group scoring more than the ASD group (Z=-1.9, p=0.06). There was no significant difference between the CM group and the SPD group on the number of positively endorsed items on the SPD subscale of the SCID-II (Z=-0.42, p=0.67).

3.4.2: Clinical characteristics

3.4.2.1: Autistic traits

Autism Diagnostic Observation Schedule (ADOS)

The ADOS domain scores for each group of participants are given in Table 3.2.

	ASD	*SPD*	*CM*	*Controls*
ADOS comm	3 (2)	1 (2)	2 (1)	0 (0)
ADOS SI	5 (1)	2 (2)	5 (3)	0 (0)
ADOS Imag	1 (2)	0 (0)	0 (1)	0 (0)
ADOS SBRI	1 (1)	0 (1)	0.5 (1)	0 (0)

Table 3.2: Participant ADOS scores given as median (inter-quartile range)
ADOS comm –communication score; ADOS SI –social interaction score; ADOS Imag – imagination score; ADOS SBRI – stereotyped behaviours and repetitive interests score

The Kruskal Wallis test shows that significant differences exist between the groups for each of the domains (Chi sq = 19.1 – 74.5, p<0.0001 for all domains). Follow-up Mann Whitney U tests revealed significant differences between each of the affected groups and the controls (all p < 0.05) as well as significant differences between the ASD and the SPD group on all 4 domains (Z= -2.2 – -4.2, all p < 0.04).

Compared to the ASD group the CM group showed a trend towards significantly greater social impairment (as reported above, Z=-1.8, p=0.06) but significantly less impairment in imagination (Z=-2.1, p=0.04). No difference was seen between the ASD group and the CM group in terms of communication or stereotyped behaviours / repetitive interests.

As would be expected the CM group were significantly more impaired compared to the SPD group with respect to the communication and social domains (Z=-3.0, p=0.003 and Z=-4.4, p<0.001 respectively). However no significant differences were seen between the CM and SPD groups in imagination or stereotyped behaviours / repetitive interests (Z=-0.7, p=0.47 and Z=-0.8, p=0.5 respectively).

In order to assess whether the differences between the groups may be confounded by IQ differences between the groups, Spearman's correlations were run between full-scale IQ and the ADOS domains within each group. No significant correlations were seen for any domain in any group suggesting that in these groups IQ does not significantly relate to

the degree of autistic traits. Group differences in IQ are therefore unlikely to account for the differences in ADOS scores that are reported.

Autism Spectrum Quotient (AQ) and Empathy Quotient (EQ)

The AQ and EQ scores for the groups are summarised in Table 3.3 and Figures 3.2 – 3.3.

	ASD	*SPD*	*CM*	*Controls*
AQ total	33.5 (9.5)	23.9 (11.8)	34.8 (7.6)	11.8 (6.1)
Social skills	7.3 (2.4)	4.6 (2.7)	6.9 (2.5)	1.4 (1.8)
Ab. to switch	7.9 (2.0)	5.4 (3.1)	9.3 (0.8)	3.3 (1.9)
Att. to detail	6.4 (2.4)	5.2 (2.4)	6.0 (1.9)	3.3 (2.6)
Comm	6.3 (2.6)	4.0 (3.2)	7.6 (2.1)	1.7 (1.5)
Imag	5.4 (2.7)	4.8 (2.2)	5.0 (2.9)	2.1 (1.8)
EQ total	31.4 (13.0)	46.7 (10.8)	30.5 (8.7)	56.8 (13.9)

Table 3.3: AQ and EQ scores given as mean (standard deviation)

The total AQ score differed significantly between the groups (F=34.5, p<0.001) with follow up t-tests revealing significant differences between the controls and the other 3 groups (all p < 0.001). The SPD group scored significantly less than the ASD or CM groups (p<0.001 and p=0.001 respectively). There was no significant difference between the ASD and CM groups (p=0.69).

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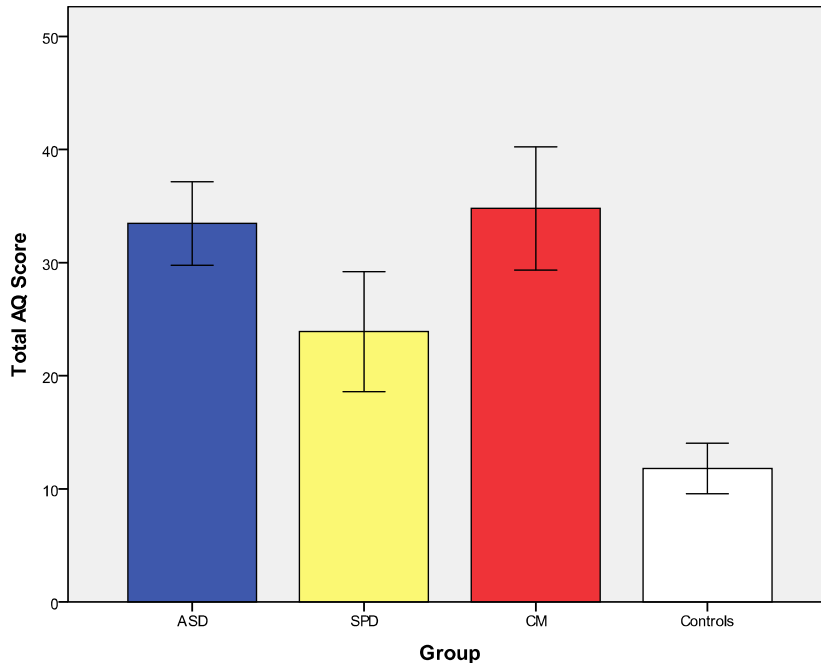
Figure 3.2: Mean and 95% CI for AQ scores in participant groups

An exploratory analysis of the subscales of the AQ was conducted. For the social and communication skills subscales the pattern of results was the same as the total score. For the ability to switch subscale the pattern was also similar expect there was a trend towards the CM group being significantly more impaired than the ASD group (p=0.09). For the attention to detail subscale the pattern was also similar to that found for the total score expect the difference between the CM group and the SPD group was less marked and non-significant (p=0.25). For the imagination subscale, the controls showed less impairment than the other groups (all p <0.001); however there were no significant differences between the ASD, SPD or CM groups (all p>0.25).

When IQ was added as a covariate to the above the results did not alter significantly for the total scores or for the social, communication or imagination subscales of the AQ. For

the ability to switch subscale, the difference between the CM and ASD groups became significant (p=0.04) whereas for the attention to detail subscale the difference between the ASD and SPD group became less marked although a trend towards significance remained apparent (p=0.054).

A similar pattern of results was seen for the total EQ score with a significant main effect of group (F=24.8, p<0.001) and significant differences between controls and the other three groups (all p<0.001), as well as between the SPD group and the ASD and CM groups (p<0.001 and p<0.01 respectively). No significant difference was seen between the ASD and CM groups (p=0.84).
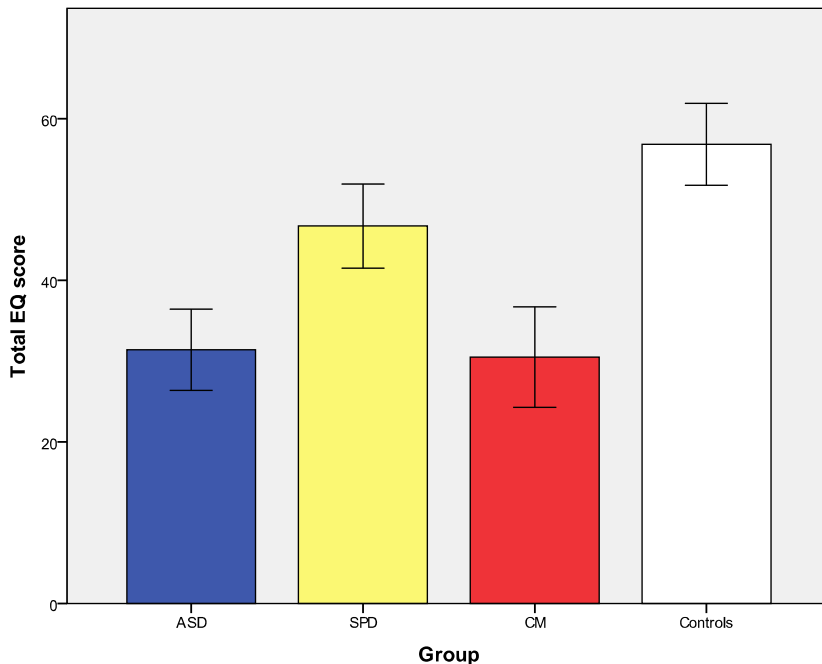
Figure 3.3: Mean and 95% CI of EQ scores in participant groups

Autism Diagnostic Interview (ADI)

ADI scores were only available on a limited number of participants (10 individuals with ASD, 8 with SPD and 2 from the CM group). The CM group was therefore not considered further. The results for the ASD and SPD groups are summarised in Table 3.4 and Figure 3.4.

	ASD	*SPD*
ADI past / ever		
Social Interaction	10.0 (12.0)	2.0 (4.0)
Communication	9.5 (6.0)	5.0 (2.0)
Repetitive Behaviours	3.0 (3.0)	1.0 (2.0)
ADI current		
Social Interaction	5.0 (8.0)	1.0 (6.0)
Communication	6.0 (5.0)	4.0 (2.0)
Repetitive Behaviours	3.0 (2.0)	1.0 (2.0)

Table 3.4: ADI scores for diagnostic and current behaviour algorithms

When the diagnostic (past / ever) algorithm of the ADI was considered there were significant differences between the ASD and SPD groups in the communication and repetitive behaviour sub-domains (Z=-2.2, p=0.03; Z=-2.6, p=0.01 respectively) and there was a trend towards a significant difference in the social interaction sub-domain score (Z=-1.92, p=0.054). When the current behaviour algorithm was used there was a significant difference between the groups in the repetitive behaviour sub-domain (Z=-2.7, p=0.07); however, there were no significant differences between the groups in either social interaction or communication (Z=-1.05, p=0.29; Z=-0.18, p=0.86 respectively).
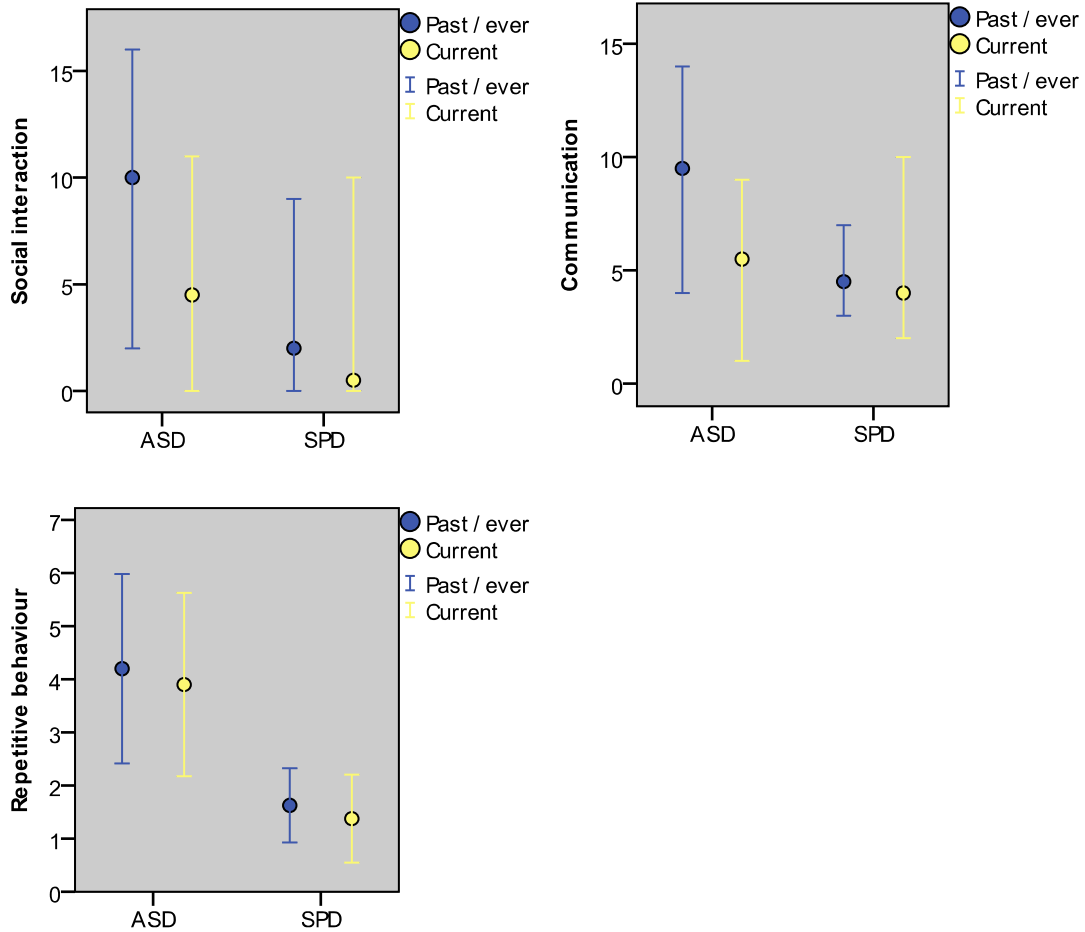
Figure 3.4: Graphs showing median and 95% CI for ADI past / ever and current scores

3.4.2.2: Schizotypal / psychotic traits

SCID – II psychosis related categories

The ratings of each of the groups in relation to the three SCID-II schizophrenia spectrum related personality disorder categories are given in Table 3.5.

	ASD	*SPD*	*CM*	*Controls*
Paranoid				
Diagnosis	0 (0%)	3 (14.3%)	2 (20%)	0 (0%)
Traits	0.5 (2.0)	2.0 (2.0)	2.0 (2.0)	0.0 (0.0)
Score	9.0 (4.0)	13.0 (6.0)	14 (6.0)	7.0 (0.0)
Schizotypal				
Diagnosis	0 (0%)	21 (100%)	10 (100%)	0 (0%)
Traits	2.0(2.0)	5.0 (1.0)	5.0 (2.0)	0.0 (0.0)
Score	15.0 (5.0)	22.0 (2.0)	21.0 (4.0)	9.0 (1.0)
Schizoid				
Diagnosis	2 (7.1%)	2 (9.5%)	1 (10%)	0 (0%)
Traits	1.0 (2.0)	1.0 (2.0)	2.0 (1.0)	0.0 (0.0)
Score	9.0 (4.0)	9.0 (4.0)	12.0 (4.0)	7.0 (0.0)

Table 3.5: Ratings on SCID-II schizophrenia spectrum related personality disorder categories.

Diagnosis – number (percentage) who meet diagnostic criteria; traits – median (IQR) for number of traits endorsed for each category; score – median (IQR) of total score for each category (see methods for derivation)

There was a significant difference between the groups with respect to the diagnosis of paranoid personality disorder (Fishers exact test = 8.9, p=0.006, no significant differences between O and E for any group) but not for the diagnosis of schizoid personality disorder (Fishers exact test = 3.7, p=0.23).

For the number of endorsed traits and the total score, significant differences were seen between the groups with respect to all three SCID- II categories (chi sq = 28.2 to 73.0, all

p<0.001 for both traits and score). For each of the categories examined the controls scored significantly less than the other three groups (Z=-2.1 to -6.6, p<0.001 to 0.03)

With regard to schizotypal personality disorder the ASD group scored less than the SPD group (traits: Z=-6.0, p<0.001; score: Z=-5.9, p<0.001) and the CM group (traits: Z=-4.7, p<0.001; score: Z=-4.6, p<0.001). This would be expected given this measure was used to define the groups. There were no differences between the SPD and CM groups (traits: Z=-0.51, p=0.61; score: Z=-0.04, p=0.97).

For paranoid personality disorder the ASD group scored less than either the SPD group or the CM group (traits: Z=-2.9, p=0.003; score: Z=-3.1, p=0.002 and traits: Z=-2.2, p=0.03; score Z=-2.6, p=0.009 respectively). Again no significant differences were seen between the SPD and the CM group (traits: Z=-0.17, p=0.87; score Z=-0.75, p=0.46).

For schizoid personality disorder there were no significant differences between the ASD group and the SPD group in terms of either the number of traits endorsed or their total scores (Z=-0.17, p=0.87; Z=-0.670, p=0.51 respectively). However, the ASD group scored significantly less than the CM group (traits: Z=-2.1, p=0.04; score Z=-2.1, p=0.03). Similarly the SPD group also scored significantly less than the CM group with respect to score, although not for the number of traits endorsed (traits: Z=-1.6, p=0.12; score Z=-2.3, p=0.02).

Structured Interview for Schizotypy (SIS)

The scores for the SIS are shown in Table 3.6 and illustrated in Figure 3.5.

	ASD	*SPD*	*CM*	*Controls*
Positive	5.0 (4.0)	15.5 (7.0)	16.0 (9.0)	3.0 (3.0)
Negative	9.5 (7.5)	9.0 (7.5)	12.0 (5.0)	2.0 (2.0)
Disorganised	3.0 (3.0)	3.0 (2.5)	4.0 (2.0)	0 (0)

Table 3.6: Schizotypal traits as measured by the SIS in each of the groups

Results given as median (IQR)

Significant differences between the groups were identified using the Kruskal-Wallis test for positive, negative and disorganised symptoms (chi sq=47.6, p<0.001; chi sq=43.7, p<0.001 and chi sq= 50.5, p<0.001 respectively).
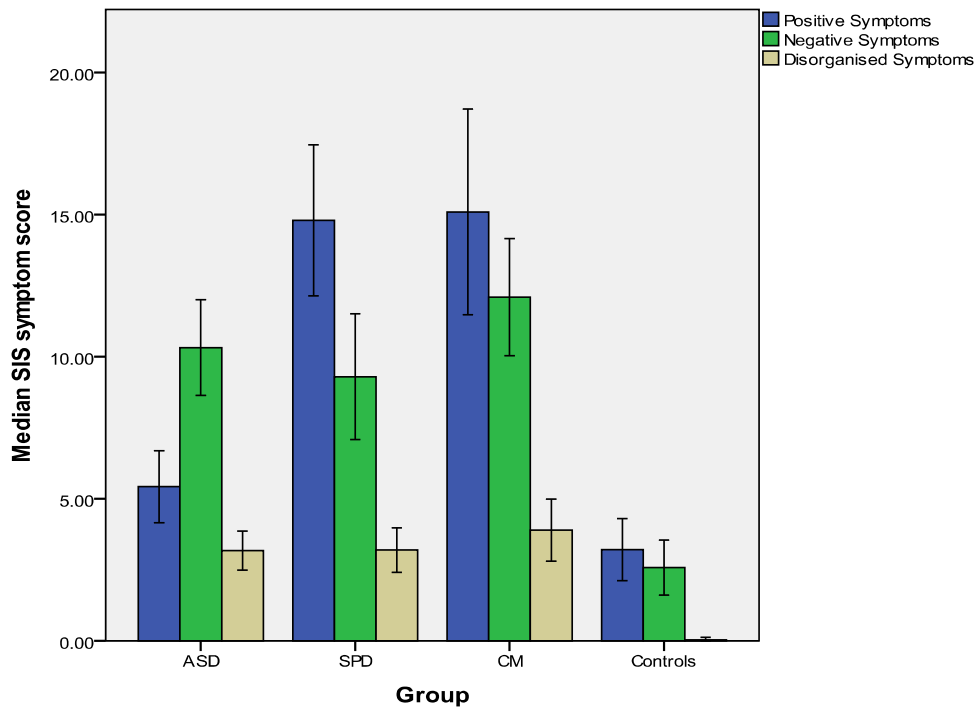
Figure 3.5: Median (and 95%CI) of reflected SIS scores for positive, negative and disorganised symptoms in each group

Follow-up Mann Whitney tests showed that the controls scored less than the other three groups in all areas of the SIS (Z=-2.8 to -6.2; p=0.005 to <0.001). In addition, with regard to positive symptoms, individuals with ASD scored less than the SPD or CM groups (Z=-4.8, p<0.001; Z=-4.17, p<0.001 respectively) whereas the SPD group did no differ from the CM group (Z=-0.00, p=1.0). In contrast there were no significant differences between the ASD group and the SPD or CM groups with respect to negative symptoms (Z=-0.9, p=0.38; Z=-1.3, p=0.19 respectively) or disorganised symptoms (Z=-0.06, p=0.95; Z=-1.2, p=0.21 respectively). The CM group did however show a trend towards significantly greater levels of negative symptoms than the SPD group (Z=-1.9, p=0.06) although not disorganised symptoms (Z=-1.11, p=0.26).

Positive and Negative Syndrome Scale (PANSS)

The scores for the PANSS positive and negative symptom scales are shown in Table 3.7 and Figure 3.6. Breakdowns for the individual symptoms within the positive and negative symptom categories are given in Tables 3.8 - 3.9 and Figures 3.7 – 3.8. For each individual symptom measure, when the summary statistic (chi sq or Fishers exact test) was significant the standardised residuals were checked to look for significant differences between the observed (O) and expected (E) values for those who scored more than 2 for the symptom

	ASD	*SPD*	*CM*	*Controls*
Positive	10 (4)	13 (4)	14 (1)	7 (0)
Negative	9 (4.5)	9 (3)	11.5 (8)	7 (0)

Table 3.7: PANSS scores in each of the groups

Results give as median (IQR)
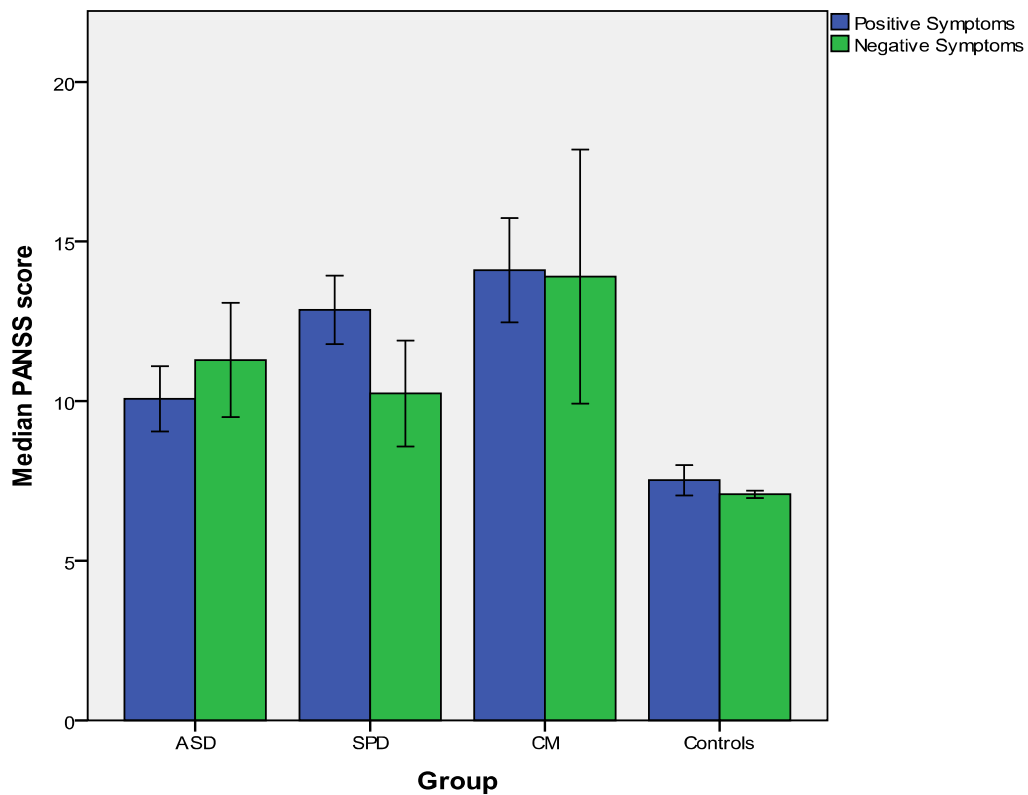
**Figure 3.6:** Median and 95% CI of PANSS scores in each group

The Kruskal-Wallis test indicated that there were significant differences between the groups for the total number of positive and negative symptoms (chi sq = 49.3, p<0.001 and chi sq = 41.7, p<0.001 respectively). The controls scored less than the other three groups on both measures (all p<0.001). The ASD group scored less than the SPD or CM

groups on positive symptoms (Z=-3.34, p=0.01; Z=-3.7, p<0.001 respectively) while there was no difference between the SPD and CM groups in this regard (Z=-1.6, p=0.1). With respect to negative symptoms, there was no difference between the ASD and SPD group (Z=-0.82, p=0.41); however the CM group scored significantly more than the SPD group (Z=-2.0, p=0.04) and showed a trend towards a significantly higher score than the ASD group (Z=-1.7, p=0.09).

	ASD	*SPD*	*CM*	*Controls*
Delusions	3.6	47.4	70	0
Conceptual Disorg	35.7	36.8	26.2	0
Hallucinations	3.6	78.9	70	0
Hyperactivity	14.3	5.3	10	0
Grandiosity	28.6	0	0	0
Suspiciousness	7.1	42.1	30	0
Hostility	3.6	0	10	0

Table 3.8: Percentage of individuals within each group scoring more than 2 on PANSS positive items

Significant differences in the individual positive symptom scores were seen for delusions (Fisher's exact test = 29.3, p<0.001, O>E for SPD and CM, O<E for ASD and controls), conceptual disorganisation (chi sq = 9.3, p=0.03, O<E for controls), hallucinations (chi sq = 45.7, p<0.001, O>E for SPD and CM, O<E for ASD and controls), grandiosity (Fisher's exact test = 11.6, p=0.001, O>E for ASD) and suspiciousness (Fisher's exact test = 15.1, p=0.001, O>E for SPD, O<E for controls)
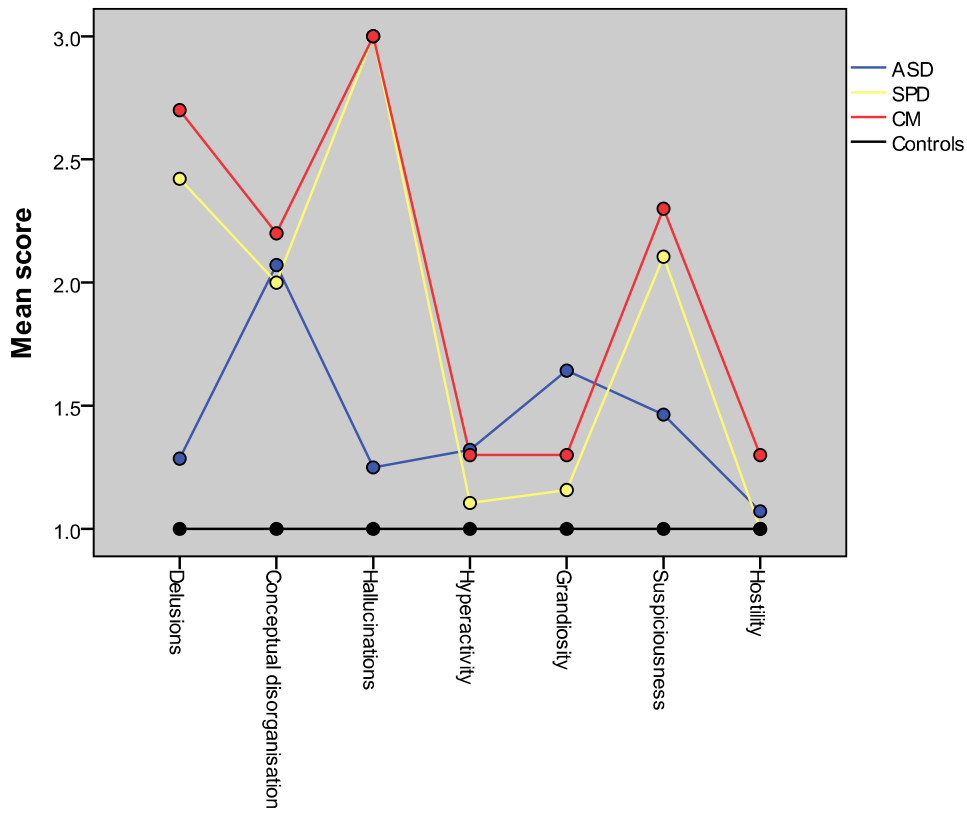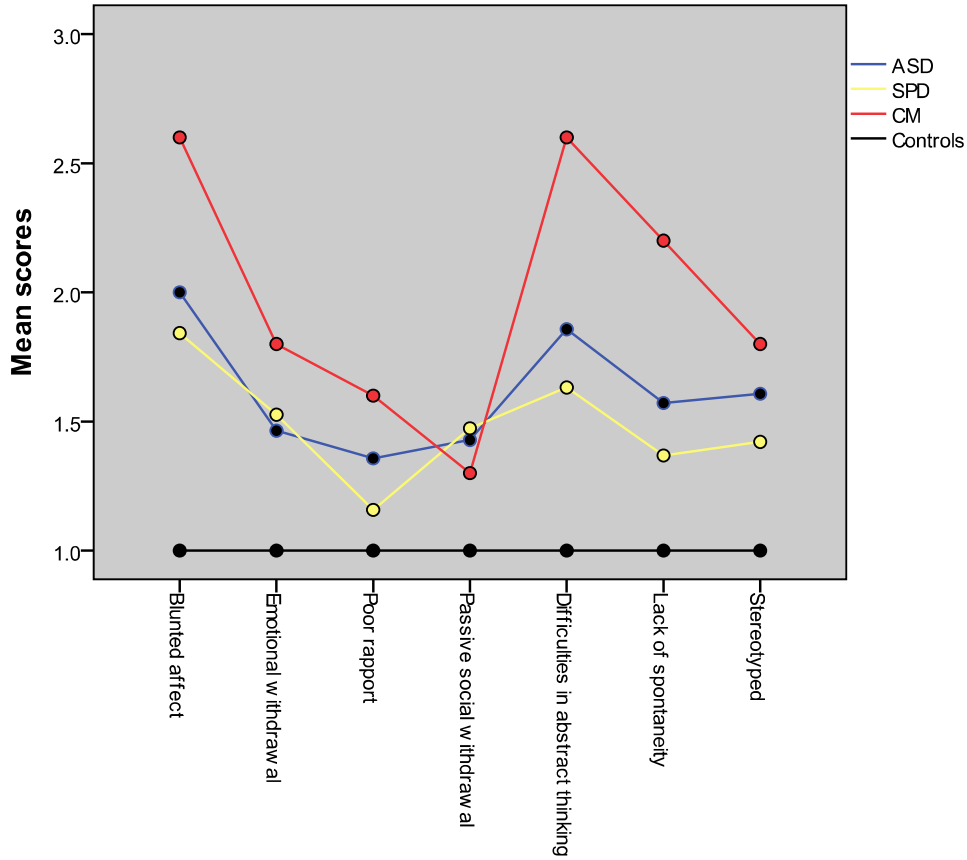
Figure 3.7: Individual symptom profile score for PANSS positive symptoms

For the individual negative symptom measures, significant differences were seen between the groups for blunted affect (chi sq = 12.6, p=0.006, O<E for controls), difficulty in abstract thinking (Fisher's exact test = 8.0, p=0.04, no significant differences between observed and expected results) and lacking spontaneity / conversational flow (Fisher's exact test = 8.0, p=0.02, O>E for CM). There was also a trend towards a significant difference for stereotyped behaviour (Fisher's exact test = 6.4, p=0.06, no significant differences between observed and expected results).

	ASD	SPD	CM	Controls
Blunted affect	35.7	31.6	60	0
Emotional wd.	17.9	15.8	30	0
Poor rapport	10.7	5.3	10	0
Passive social wd	14.3	15.8	10	0
Diff abstract think	21.4	21.1	40	0
Lack spontaneity	10.7	10.5	40	0
Stereotyped	21.4	10.5	30	0

Table 3.9: Percentage of individuals within each group scoring more than 2 on PANSS negative symptom items

Figure 3.8: Individual Symptom profile score for PANSS negative symptom scale

Peters Delusions Inventory (PDI) and Rust Inventory of Schizotypal Cognitions (RISC)

Results for the PDI and the RISC are shown in Table 3.10. Significant differences were seen between the groups using all measures of the PDI (chi sq = 17.3 to 22.8, p=0.001 to <0.001) and the total RISC score (F=6.13, p=0.001). The controls scored less than the three other groups on all of the PDI measures (all p<0.02). There were no significant differences between the ASD and the SPD group, although there was a trend towards an increased level of distress reported by the SPD group (Z=-1.8, p=0.08) whereas the ASD group scored less than the CM group on each of the measures (all p<0.02). There were no significant differences between the CM and the SPD groups (all p>0.1).

	ASD	*SPD*	*CM*	*Controls*
PDI				
Endorsed	3.0 (3.5)	4.0 (7.0)	8.0 (7.0)	2.0 (3.0)
Distress	5.5 (9.5)	10.5 (20.0)	23.0 (9.0)	2.0(4.0)
Preoccupied	7.5 (6.5)	9.0 (14.5)	21.0 (15.0)	2.0 (5.0)
Conviction	8.5 (11.5)	10.0 (15.0)	21.0 (13.0)	3.0 (7.0)
RISC	25.5 (10.5)	30.9 (13.3)	39.9 (10.6)	22.9 (9.7)

Table 3.10: PDI and RISC scores in each of the groups

PDI scores are given as median (IQR); RISC scores are given as mean (standard deviation)

For the RISC, follow-up t tests showed that the SPD group scored significantly more than the controls ($p=0.01$) but not the ASD group ($p=0.1$) who in themselves did not differ significantly from the controls ($p=0.37$). In contrast, the comorbid group scored significantly more than any of the ASD, SPD or control groups ($p=0.002$, $p=0.05$ and $p<0.001$ respectively) (Figure 3.9).
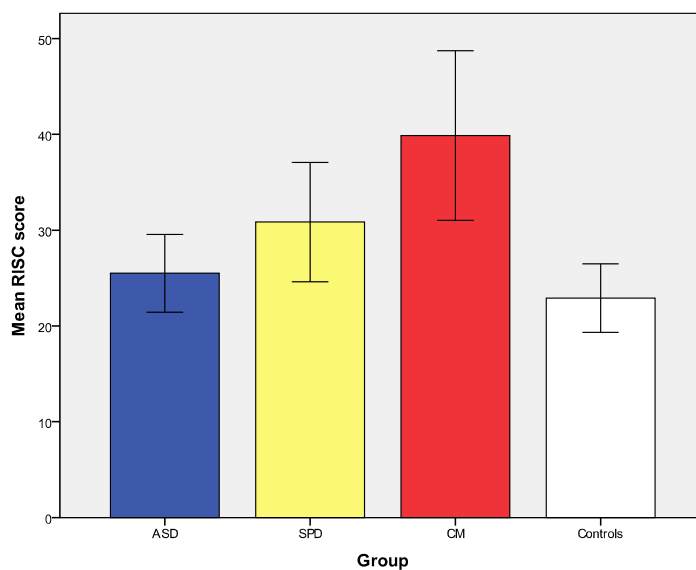
Figure 3.9: Bar chart showing mean and 95% CI for RISC scores in each group

3.4.2.3: General psychiatric symptomatology

Obsessive-compulsive symptoms

The results for the Florida Obsessive Compulsive Inventory (FOCI) are shown in Table 3.11. There were significant differences between the groups with respect to the scores on the FOCI for both the number of symptoms endorsed and the severity of these symptoms (chi sq = 18.7, p<0.001; and chi sq = 25.6, p<0.001 respectively).

	ASD	*SPD*	*CM*	*Controls*
Endorsed	3.5 (5.5)	4.5 (9.5)	4.5 (3.0)	0.0 (2.0)
Severity	5.0 (7.5)	5.0 (8.0)	7.0 (4.0)	0.0 (2.0)

Table 3.11: FOCI scores in each group; given as median (IQR)

The ASD, SPD and CM groups all scored significantly less than the controls on both measures (all p<0.003). There were no significant differences between the ASD and SPD groups on endorsed symptoms or severity (Z=-1.2, p=0.23; Z=-0.18, p=0.86 respectively). The CM group did not differ significantly from the ASD or SPD groups with respect to the number of symptoms endorsed (Z=-1.06, p=0.29; Z=-0.25, p=0.80 respectively) but did show trends towards significantly greater severity of symptoms (Z=-1.94, p=0.052; Z=-1.70, p=0.09 respectively).
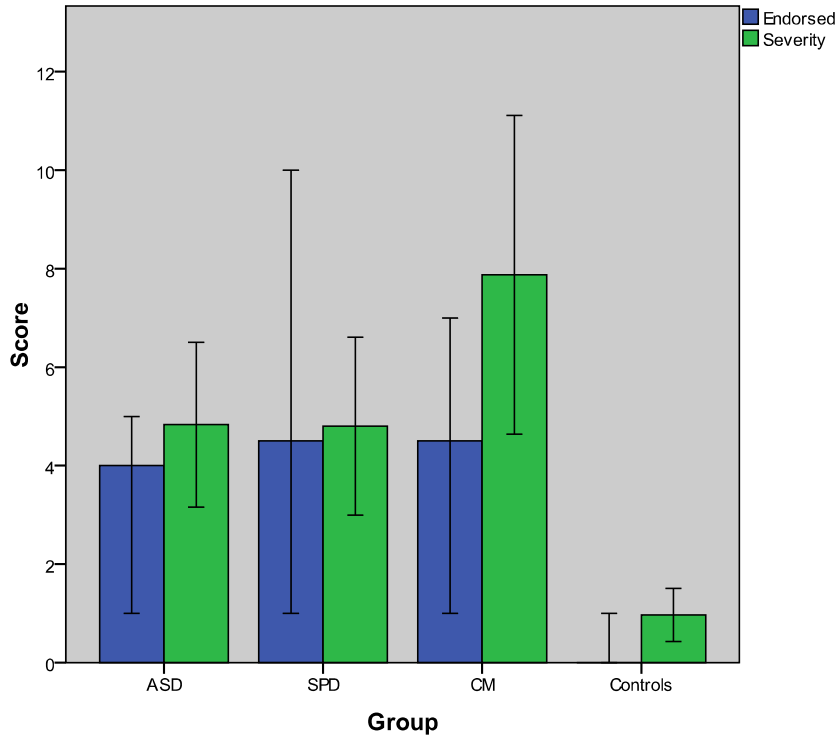
Figure 3.10: Median and 95% CI for FOCI scores in each group

Positive and Negative Syndrome Scale: general symptoms

The median and interquartile range for the PANSS general symptom score is given in Table 3.12 and the percentages of each group who score more than 2 on the individual symptoms are shown in Table 3.13. As was done for the PANSS positive and negative symptoms scales, for each individual symptom measure, when the summary statistic was significant the standardised residuals were checked to look for significant differences between the observed (O) and expected (E) values for each group.

	ASD	*SPD*	*CM*	*Controls*
General	21.5 (6.0)	21.0 (5.0)	25.5 (8.0)	16.0 (1.0)

Table 3.12: Total PANSS general symptoms shown as median (IQR)

The ASD, SPD and CM groups all scored more highly than the controls with respect to total symptoms (all p<0.001). The CM group scored significantly more than the ASD group and there was a trend towards significance compared to the SPD group on the total PANSS general symptom score (Z=-2.7, p=0.005; Z=-1.7, p=0.09 respectively).

	ASD	*SPD*	*CM*	*Controls*
Somatic concern	0	15.8	0	0
Anxiety	32.1	36.8	40	0
Guilt	14.3	21.1	30	0
Tension	7.1	26.3	20	6.7
Mann / post	10.7	5.3	10	0
Depression	32.1	36.8	80	0
Motor retardation	10.7	5.3	10	0
Uncooperativeness	0	0	0	0
Unusual thoughts	21.4	36.8	60	0
Disorientation	0	0	0	0
Poor attention	3.6	0	0	0
Lack judge / insight	3.6	10.5	10	0
Disturbed volition	21.4	16.7	10	0
Impulsive	7.1	0	10	0
Preoccupation	32.1	21.1	30	0
Active avoidance	28.6	42.1	80	0

Table 3.13: Percentage of individuals in each group scoring 3 or more on individual items of the PANSS general symptoms subscale

Significant differences between the groups for individual symptoms were seen for anxiety (Fishers exact test = 9.0, p=0.02, O<E for controls), depression (chi sq = 17.4, p=0.001, O<E for controls, O>E for CM), unusual thought content (Fishers exact test = 13.0, p=0.003, O<E for controls, O>E for CM), and active social avoidance (chi sq = 18.2, p<0.001, O<E for controls, O>E for CM); trends towards significant differences were seen for somatic worry (Fishers exact test = 5.4, p=0.052, O>E for SPD), guilt (Fishers exact test = 6.8, p=0.053, no significant differences between O and E for any group) and preoccupation (Fishers exact test = 7.1, p=0.06, no significant differences between O and E for any group).

Psychiatric diagnoses

The retrospectively reported lifetime prevalence of SCID I anxiety, depressive and psychotic disorders are shown in Table 3.14. Simple phobias are not included in the analysis and social phobias are considered separately due to their particular status within the conditions under study.

	ASD	*SPD*	*CM*	*Controls*
Any disorder	60.7	66.7	100	12.1
Social phobia	42.9	28.6	40.0	0.0
OCD	10.7	4.8	20	0.0
Other anx. dis.*	14.3	33.3	40	0.0
Depression	35.7	57.1	90.0	12.1
Brief psychosis	0.0	14.3	20.0	0.0

Table 3.14: Lifetime psychiatric disorders as diagnosed using SCID-I

There were significant differences between the groups for the lifetime prevalence of any psychiatric disorder (chi sq = 32.5, p<0.001, O>E for CM, O<E for controls), social phobia (chi sq = 17.6, p<0.001), p=0.001, O>E for ASD, O<E for controls), other anxiety disorders (Fishers exact test = 16.4, p<0.001, O<E for controls), depressive disorders (chi sq = 24.2, p<0.001, O>E for CM, O<E for controls) and brief psychotic episodes (Fishers exact test = 7.1, p=0.01, O>E for CM). There was a trend towards a difference for OCD (Fishers exact test = 6.1, p<0.05, no significant differences between O and E for any group).

Self-reported lifetime psychiatric diagnoses

When individuals were asked about their past psychiatric treatment, six (21%) individuals with ASD, eight (36%) individuals with SPD and four (40%) CM individuals reported having received previous treatment for depression; three (11%) individuals with ASD, two (9%) individuals with SPD and no (0%) CM individuals reported previously receiving treatment for an anxiety disorder; and two individuals with SPD (9%) and three (30%) CM individuals reported receiving treatment for psychosis.

Personality Disorder Clusters

Table 3.15 shows the prevalence of Cluster B (borderline, dissocial, narcissistic and histrionic) and Cluster C (avoidant, dependent and obsessive-compulsive) personality disorders in the four groups.

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	ASD	SPD	CM	Controls
Cluster B	7.1	4.8	30	0
Cluster C	57.1	33.3	90	0

Table 3.15: Percentage of individuals in each group who meet criteria for one or more Cluster B or Cluster C personality disorders

There were significant differences between the groups for both cluster B and C personality disorders (Fishers exact test = 8.5, p=0.01, O>E for CM; chi sq = 37.5, p=<0.001, O>E for ASD and CM, O<E for controls).

3.4.2.4: Relationships between schizotypal and autistic traits

A summary of the correlations between the domains of the SIS and the total scores for the AQ and EQ in each group are given in Table 3.16 and Figures 3.11 – 3.13.

|	ASD		SPD		CM		Controls	
	AQ	EQ	AQ	EQ	AQ	EQ	AQ	EQ
SISpos	-0.15 (0.44)	-0.28 (0.15)	**0.46 (0.047)**	-0.34 (0.17)	0.26 (0.48)	-0.37 (0.30)	0.08 (0.70)	-0.30 (0.15)
SISneg	0.25 (0.21)	-0.33 (0.09)	**0.62 (0.005)**	-0.18 (0.48)	-0.06 (0.88)	-0.55 (0.88)	0.25 (0.24)	-0.33 (0.12)
SISdis	**-0.39 (0.04)**	**0.46 (0.02)**	**0.45 (0.05)**	-0.10 (0.71)	-0.33 (0.36)	-0.33 (0.36)	-0.26 (0.23)	-0.29 (0.17)

Table 3.16: Correlation coefficients between schizotypal and autistic traits in each group. Results are given as rho (p); statistically significant results are highlighted in bold

A statistically significant correlation was seen between the total AQ score and the positive domain of the SIS only in the SPD group (Figure 3.11). No significant difference was seen between the groups in their AQ-positive symptom correlations when all the groups were considered together, however when only the SPD and ASD group were examined there was a trend towards a significant interaction (p=0.09).
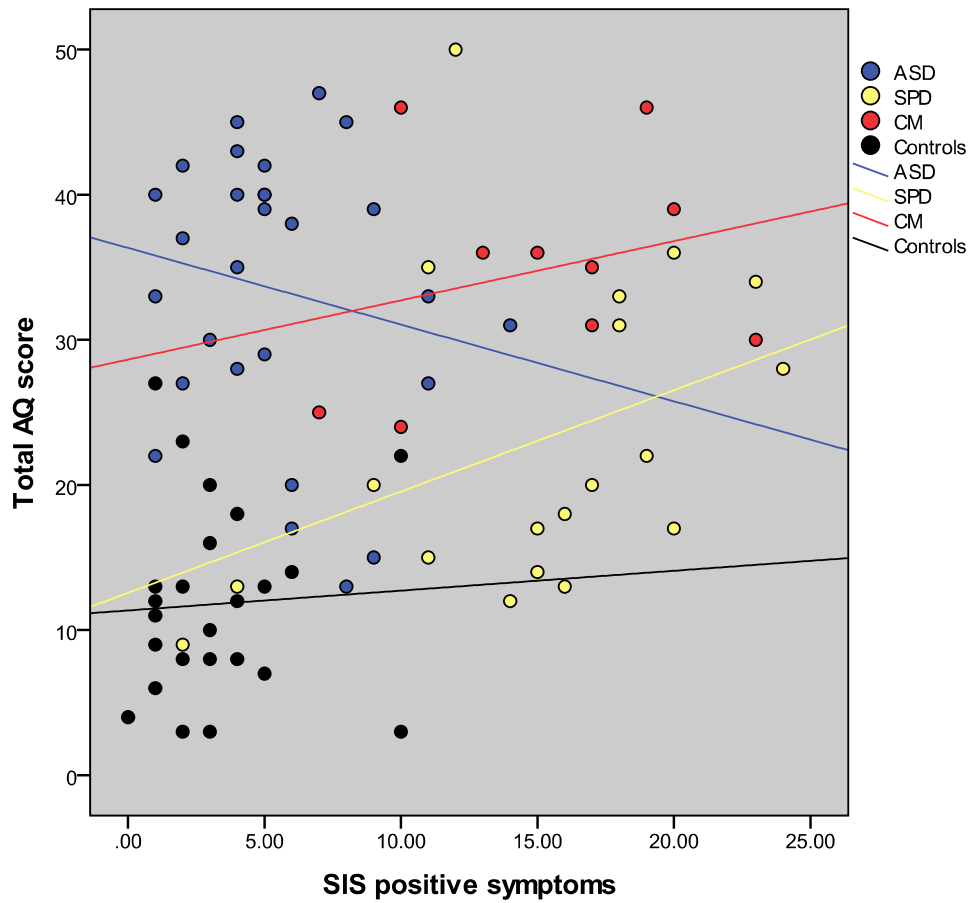
**Figure 3.11**: Relationship between positive schizotypal traits and autistic traits in each group

Negative symptoms as measured by the SIS were significantly correlated with the AQ score in the SPD group and there was a trend towards a significant correlation in the ASD group (Figure 3.12). No significant difference in the AQ-negative symptoms correlations was seen between the groups (p=0.59).
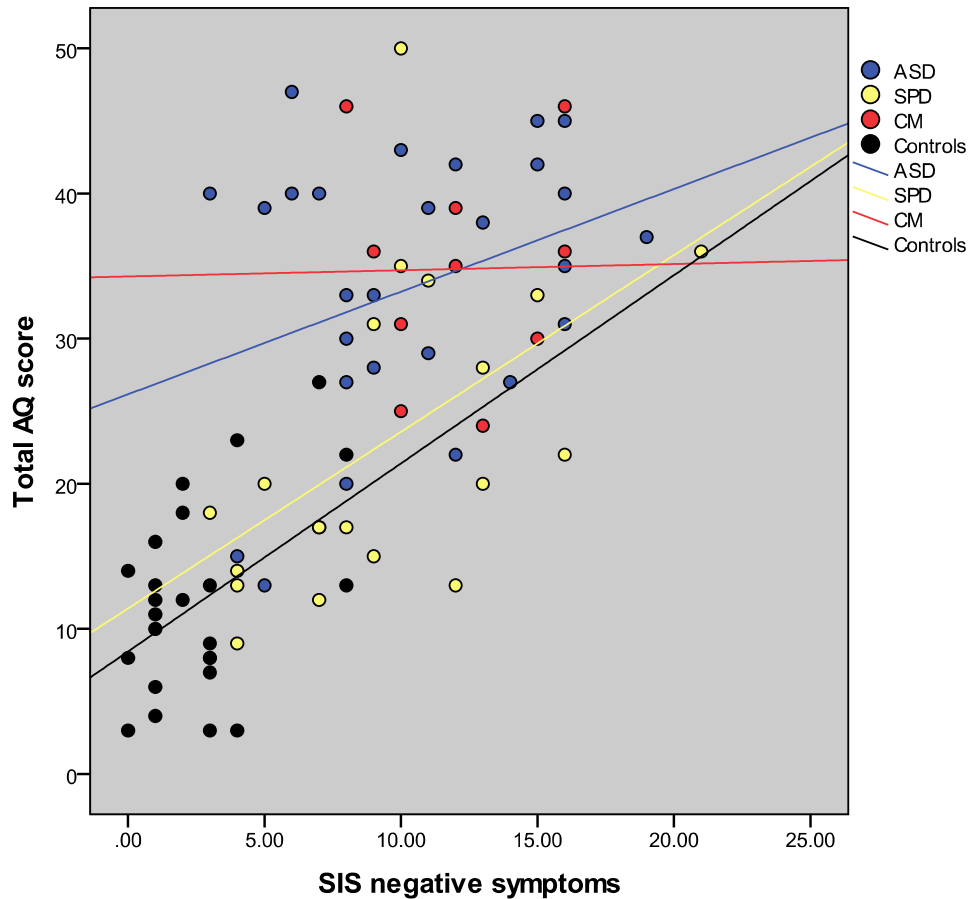
Figure 3.12: Relationship between negative schizotypal traits and autistic traits in each group

For disorganised symptoms there was a statistically significant negative correlation in the ASD group (i.e. more disorganised symptoms were associated with fewer autistic traits), whereas this relationship was reversed in the SPD group (Figure 3.13). There was a

significant difference between the groups in terms of the AQ-disorganised symptoms correlation (p=0.04).   As the spread of disorganised symptoms was very low in the controls this test of interaction was repeated with the controls excluded and it remained statistically significant (p=0.046).
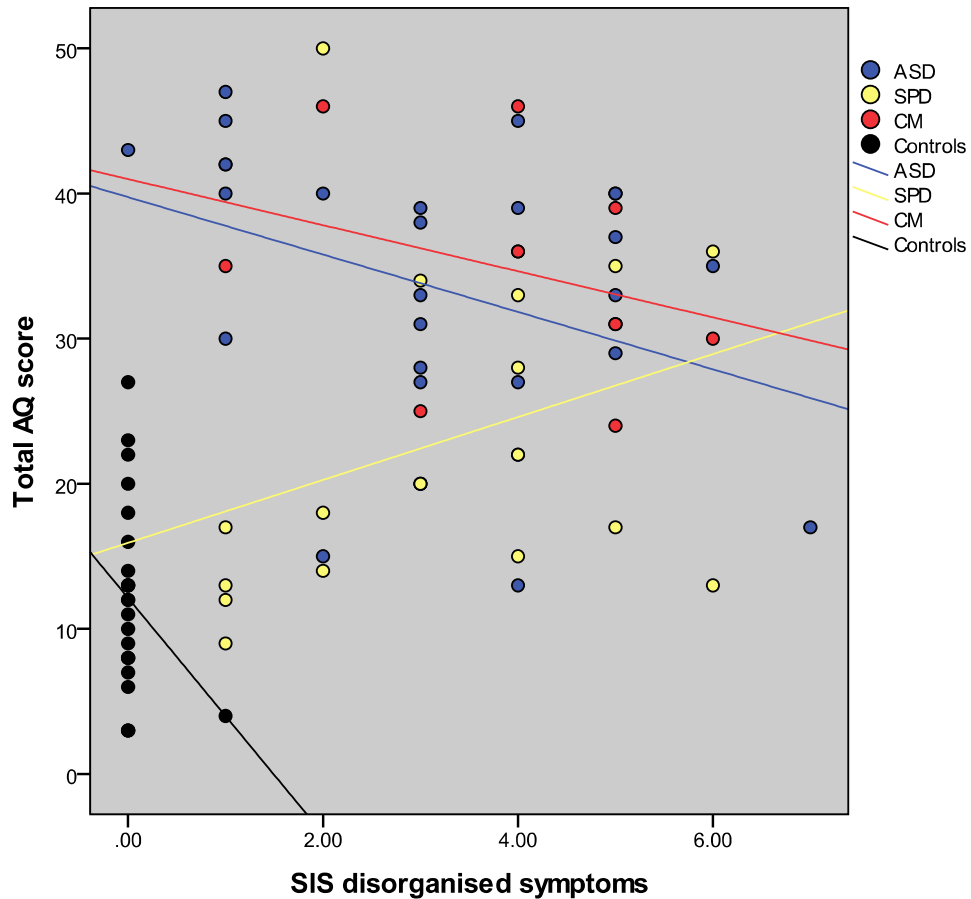
Figure 3.13: Relationship between disorganised schizotypal traits and autistic traits in each group

3.5: DISCUSSION

In this detailed clinical investigation it was found to be possible to ascribe a diagnosis of SPD or ASD to the majority of individuals using the ADOS and SCID-II suggesting that, in most cases, standardized diagnostic instruments can clinically distinguish between ASD and SPD. However, a significant minority (17%) of individuals met criteria for both ASD and SPD, despite never having received this dual diagnosis. In addition, those who met criteria for only ASD showed more traits of SPD than were seen in controls and vice versa. Negative symptoms in particular overlapped between the ASD and SPD groups and indeed were indistinguishable in terms of their severity and profile. Psychiatric comorbidity was high in all of the clinical groups, particularly in the CM group, and was probably under-recognised.

Overlap between the spectrums

Although there were some significant differences between the groups, there were marked overlaps, particularly with regard to negative and obsessive-compulsive symptoms, and each group showed features of the other condition to a greater degree than was found in controls. Broadly speaking this was true, regardless of whether the measures were self-rated, such as the AQ, EQ, PDI or RISC, or observer rated, such as SIS or PANSS, suggesting that it is a robust finding. In addition, although the majority of individuals could be placed in one or the other diagnosis, it was not possible to classify approximately 17% of the clinical sample to either condition alone. Taken together these results are consistent with the idea that ASD and SPD represent two separate but related

conditions (Carroll and Owen 2009; Craddock and Owen 2010; Cross-Disorder Group of the Psychiatric Genomics, Smoller et al. 2013).

Although the most parsimonious explanation of the data is that the conditions are related, it is far from certain that the overlaps in clinical features are actually the result of shared aetiological or pathophysiological factors – it may be that the behavioural characteristics are similar but the underlying pathology is not. The greatest overlap between the groups is in relation to negative symptoms; in addition to a similar total score, the similarity in the symptom profile is striking (Figure 3.8) and suggestive that these features are arising from similar mechanisms between the groups. Consistent with this idea, the relationship between autistic traits and negative schizotypy does not differ significantly between the groups. Although positive symptoms were most severe in the SPD and CM groups, the ASD group also showed higher levels than were found in controls. However, the profile of positive symptoms (Figure 3.7) appears to differ markedly between the groups with the ASD group having peaks in conceptual disorganisation and grandiosity, whereas the SPD and CM groups have peaks in delusions, hallucinations and suspiciousness. In addition, there was some evidence that the relationship between autistic traits and positive symptoms differed between the groups, such that within the SPD group and the CM group (although the latter was not significant) increasing autistic traits were associated with increasing positive symptoms, whereas no relationship was seen in the ASD group. Disorganised schizotypy also showed different relationships with autistic traits between the groups, with the ASD and CM group having negative relationships, while the SPD group showed a positive relationship. This set of correlations suggests that although

negative symptoms likely arise out of similar mechanisms regardless of group (and may in fact be simply a different way of describing autistic traits), this is not the case for positive and disorganised symptoms.

The finding that 17% of the clinical sample met standardised criteria for both ASD and SPD is in keeping with Anckarsater et al (2006) who reported that the prevalence of SPD in individuals with Asperger Syndrome was 23.4%. Interestingly, in the CM group the relationship between autistic traits and positive symptoms was most similar to that of the SPD group, whereas greater similarity to the ASD group was seen for the relationship between autistic traits and disorganised symptoms. This would suggest that rather than having a particularly severe form of one or the other condition, individuals who meet criteria for both disorders may have aspects of both.

Notably, from a clinical perspective, the CM group are clearly a highly morbid group, who are more severely affected across multiple autistic, schizotypal and general psychiatric domains than those affected by one disorder alone; indeed in the current sample all of the CM individuals met SCID-I criteria for a psychiatric disorder at some point in their lives. In routine clinical practice it is unusual to make a dual diagnosis of ASD and SPD, indeed they are generally regarded as mutually exclusive (American Psychiatric Association 2000) and none of the current sample had previously received both diagnoses. The current findings suggest it is important to identify both conditions when present, not only to highlight the increased severity of the disorders, but also the increased risk of psychiatric disorder. In addition, given that support strategies, service

utilisation and possibly medication prescription are likely to differ between individuals with ASD and SPD, it is important to identify those who meet criteria for both in order to ensure that their needs are adequately met.

Although it was only possible to conduct the Autism Diagnostic Interview in a limited number of participants the results suggest that the differences between SPD and ASD are more marked in early childhood and diminish with age. The past / ever algorithm of the ADI showed significantly higher levels of communication impairment and repetitive behaviours and a trend towards significantly greater social impairment in the ASD group compared to the SPD group. However, when the current behaviour algorithm was employed, there was no longer a difference in communication or social interaction impairment between the groups, with this being due to improvements in the ASD group, as opposed to deteriorations in the SPD group. This is in contrast to the hypothesis that the SPD group would experience deterioration analogous to schizophrenia and implies, that for this small sample at least, the difficulties are lifelong. The improvement seen in the ASD group suggests that cognitively able individuals with ASD may be able to learn the rules of communication and social interaction so that they are less impaired in adulthood. From a clinical perspective these findings highlight the importance of obtaining a developmental history as part of the diagnostic process for ASD and SPD although unfortunately this is not always possible in an adult population.

Psychiatric disorder in ASD and SPD

Although not an ecological study, the very high rates of comorbid psychiatric disorder identified by the SCID-I in ASD and SPD deserve comment. It is perhaps unsurprising that both groups show high rates of social phobia, but the rates for depression (ASD - 36%, SPD - 57%, CM – 90%) and other anxiety disorders (ASD - 14%, SPD - 33%, CM – 40%) are also very high. It is important to note that the SCID-I relies upon retrospective reporting of psychiatric symptoms which may bias these figures. To the author's knowledge population based studies considering psychiatric disorder in adults with ASD or SPD have not been published, however the current findings are consistent with those of Hofvander et al (2009) who reported lifetime rates of 53%, 50% and 24% for depression, anxiety disorder and obsessive-compulsive disorder respectively in their sample derived from a specialist clinic.

Interestingly, many individuals reported that they had not received a previous diagnosis or treatment for these disorders. Although this is based upon self-report and can therefore only be regarded as approximate, it does suggest that potentially treatable conditions are underdiagnosed in these populations. This may be one reason why, despite previous findings of high rates of psychiatric morbidity in adults with ASD (Hofvander, Delorme et al. 2009), their use of health services is no greater than that of the general population (Brugha, McManus et al. 2009).

Consistent with the hypothesis, the ASD, SPD and CM groups all had more obsessive-compulsive symptoms than the controls. However, contrary to expectations, there was no

difference between the groups in how distressing they found these symptoms. This highlights that people with ASD do not just present with preoccupations or enthusiasms but are at higher risk of distressing and disabling obsessive-compulsive symptoms than the general population (Leyfer, Folstein et al. 2006). Individuals who met criteria for both ASD and SPD were particularly distressed by their symptoms.

Implications of the findings

From a clinical perspective it is possible in many, but not all, cases to distinguish ASD and SPD using standardized diagnostic instruments. However, both groups show features of both conditions to a greater degree than is seen in controls. Psychiatrists and associated professionals working in both general adult psychiatry services and specialist autism services need to be alert to this and actively consider each diagnosis in suspected cases as misdiagnosis carries important implications for future support and treatment. There also exists a group of individuals who cannot be categorised on the basis of current clinical presentation into either ASD or SPD, but who instead meet criteria for both conditions. These individuals are not usually identified as having both conditions in routine clinical practice but the severe nature of their difficulties across multiple domains suggests that they should be identified and treated appropriately. Clinicians should also be alert to the high prevalence of psychiatric disorder in all three clinical groups examined, particularly given that it was largely underdiagnosed and undertreated in the current population. Finally, the results suggest that from a clinical perspective at least, there are marked overlaps between ASD and SPD. Whether the conditions and in particular their overlapping clinical features relate to common underlying psychological

and biological causes and mechanisms is currently unknown; the findings reviewed above provide some support for the idea that negative symptoms may arise from the same mechanism but that positive and disorganised symptoms do not. By considering more objective measures, which may have a closer association to brain function than observed behaviours, it may be possible to identify more definitive differences between the conditions.

Chapter 4

Experiment II

A neuropsychological comparison of ASD and SPD

4.1: INTRODUCTION

The study reported in Chapter 3 clearly indicates that there is considerable clinical overlap between ASD and SPD. However, the clinical measurement of behaviour is relatively imprecise and inherently subjective; it also represents only the external manifestation of psychobiological processes and therefore cannot distinguish between states where multiple different processes can lead to the same outcome. It is likely that greater insight into the relationship between ASD and SPD will be gained by the examination of more objective measures of brain function, such as neuropsychological testing.

As reviewed in Chapter 2, there are a number of potential areas of neuropsychological difference between ASD and SPD within the broad domains of executive function, central coherence / local-global processing and social cognition. Based on this review it was hypothesised that individuals with SPD would show impairments across sustained attention, inhibition and verbal working memory which are not seen in ASD; in contrast, tasks of generativity would reveal enhanced performance in SPD and impairments in ASD. Although the existing evidence is unclear it was also hypothesised that tasks of central coherence would show a local processing style in ASD, whereas in SPD a global processing bias would be seen. Emotion recognition was expected to be more severely affected in ASD, whereas explicit mentalising impairments were hypothesised to be common to both conditions. Individuals with SPD were expected to show a particular deficit in judging trustworthiness, such that they would be biased towards making more untrustworthy judgements.

4.2: METHODS

4.2.1: Recruitment

The recruitment process for the study is detailed in Chapter 3.1.2. All individuals who took part in the clinical assessments also completed the neuropsychological section of the study, barring one individual with SPD who did not return for the neuropsychological component of the study. The characteristics of the groups are given in table 4.1

4.2.2: Assessment

4.2.2.1: Executive function

Sustained Attention and Inhibition

The Sustained Attention to Response Task (SART) (Robertson, Manly et al. 1997) was employed in both its fixed and random forms (Johnson, Robertson et al. 2007). Figure 4.1 provides a summary of the task. In both forms, numbers between 1 and 9 were presented on a laptop screen 225 times over 4 minutes and 19 seconds. The numbers were in one of 5 different font sizes and no font size occurred more than twice in a row. Each number appeared on the screen for 250 milliseconds and was followed by a mask (a cross in a circle) for 900milliseconds seconds. Participants were asked to press the space bar for every number (Go trials) except for the number 3 (No-go trials). In order to minimise impulsive responses, they were asked to not press the space bar until the

appearance of the mask. In the fixed form of the SART, the numbers are presented in repeated cycles of a fixed ascending order (i.e. 1, 2, 3, 5, 6, 7, 8, 9, 1, 2….); in the random form the numbers are presented in a pseudorandom order. In both versions each number appears 15 times. All participants completed the Fixed SART followed by the Random SART.
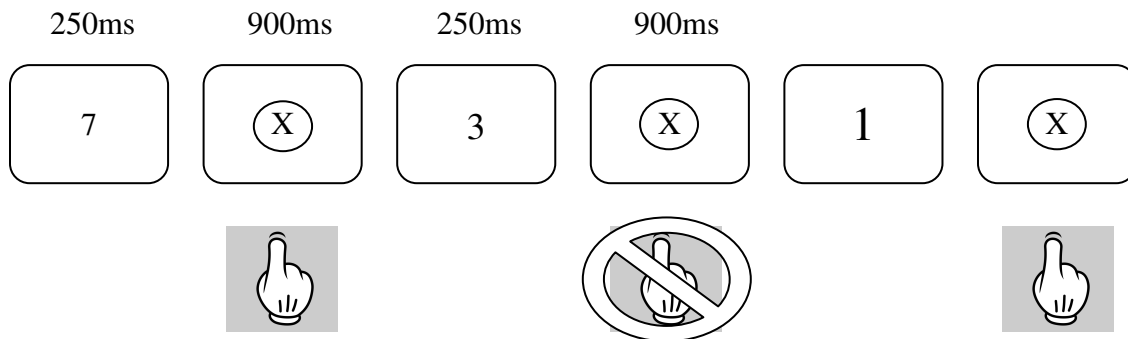
Figure 4.1: Schematic diagram of the Random SART

The SART differs from traditional continuous performance tasks in that it requires the inhibition of response to an infrequent target as opposed to requiring a response to an infrequent target. Withholding of the primed response is suggested to place greater load on sustained attention networks, which in turn allows the task to be shorter in length (Robertson, Manly et al. 1997). Clearly, in addition to sustained attention, individuals must also show intact response inhibition to perform the SART. The use of two forms, fixed and random, allows to these aspects of performance to be dissociated. The Random SART places greater load on inhibitory functions than the Fixed SART due to the random presentation of either Go or No-go trails, whereas the Fixed SART places relatively greater demand on attentional compared to inhibitory functions due to the predictable nature of the Go and No-go trials (Johnson, Robertson et al. 2007).

Performance on the SART is measured through the number of omission (failed Go-trials) and commission (failed No-go trials) errors. Omission errors on both versions of the SART are related to lapses in sustained attention. Commission errors on the random SART are related to difficulties in both sustained attention and response inhibition, whereas commission errors on the Fixed SART are primarily related to lapses in sustained attention with a much smaller load being placed upon response inhibition.

Working memory

The letter-number sequencing (LNS) tasks from the Wechsler Adult Intelligence Scale, 3rd edition (WAIS-III) was employed to test working memory. In this test, individuals are presented with a pseudorandom series of numbers and letters. They are then asked to respond with the numbers first in numerical order, followed by the letters in alphabetical order. It is considered to be a test of working memory as it requires the active manipulation of registered information prior to response (Prifitera, Saklofske et al. 2005).

The task is divided into 7 levels with gradually increasing quantities of components (ranging from level 1 which has two components – one letter and one number; to level 7 which has 8 components). Each level contains 3 items. For the current study, performance on the LNS was considered for the level reached and for the total number of correct responses.

Generativity

Generativity was measured using two tests, one of verbal fluency and one of ideational fluency.

The verbal fluency test was Benton's Controlled Word Association task (Benton 1968) commonly referred to as the FAS test. In this task individuals are first asked to produce as many words as possible beginning with the letter F in one minute; this procedure is then repeated for the letter A and the letter S. The test is scored by awarding one point for each novel real word produced (perseverative or made-up responses are not scored). The FAS test also allows some estimation of the method by which individuals produce words through the calculation of a category score (the relative number of consecutive responses to total responses that are categorically related to each other (e.g. snake, sheep and shark are all animals and as such would form one category), and phoneme scores (the relative number of consecutive response to total responses which begin with the same phoneme (e.g. apple, application, apply would form a phoneme category).

The ideational fluency test was the Use of Objects Task applied as in Turner et al (1999). In this task, participants were asked to produce as many possible uses for an object in 2½ minutes. Six objects were used, three with a clear purpose (a mug, a brick and a pencil) and three with no clear purpose (a 50cm length of dowelling, a piece of plain blue cloth measuring 110cm by 40cm and a piece of clothing elastic measuring 100cm long). For the purposeful objects the examiner gave two examples of potential uses – one established function (e.g. you can write with a pencil) and one imaginative example (e.g.

you could use a pencil to make a flagpole for a toy castle); for the non-purposeful objects one imaginative example was given (e.g. you could use the stick to turn the TV on and off). The order in which the objects were presented was counterbalanced between subjects.

The Use of Objects task was scored by awarding one point for any reasonable use of the object. In order to examine whether any of the conditions were associated with particularly creative ideas, a score for highly imaginative responses was also generated. The number of perseverative and inappropriate responses were also recorded.

4.2.2.2: Central coherence

Two tests of central coherence were employed: the block design task from the Wechsler Abbreviated Scale of Intelligence (WASI (Wechsler 1999)) and the Embedded Figures Task (EFT (Witkin 1950)).

Block design

The block design task was employed in its segmented and unsegmented forms, as was the case in Shah and Frith (1993). As described in Chapter 2, this tasks requires participants to place cubic blocks with either a white face, a red face or a half-white/half-red face together as quickly as possible to form a total of 9 designs provided in picture form by the examiner. Participants were allowed to view the design for each item throughout the item. In the standard (unsegmented) form the design is provided as a whole figure; in the segmented form it is provided divided into its constituent blocks (Figure 4.2). All

individuals completed the unsegmented form of the task prior to completing the segmented form, as to do otherwise would demonstrate to participants how they might approach the unsegmented form. To minimise practice effects the segmented and unsegmented forms were set at 90 degrees to each other.
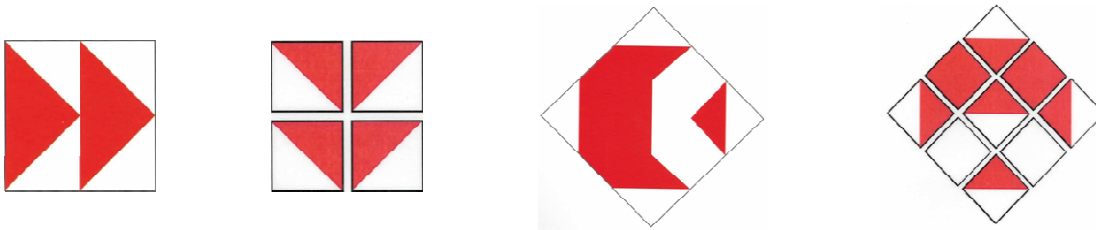

Figure 4.2: Examples of segmented and unsegmented block design stimuli

The time take until completion for each item as recorded, with a maximum time of 120 seconds for the easier designs and 180 seconds for the more difficult ones. Typically one expects individuals to perform the segmented form more quickly than the unsegmented form, with this difference being less in individuals with a local processing bias / weak central coherence. The key measure is therefore the facilitation provided by the segmented form, derived by subtracting the time to completion of the segmented form from that of the unsegmented form.

Embedded Figures Task

The Embedded Figures Task was employed in the standard fashion (Witkin 1971) (Figure 4.3). Participants were given a card with the face-up side showing a simple shape. They were informed that on the other side of the card was a complex design and they had to find the simple shape within this design as quickly as possible. When they found the

simple shape within the complex design they were to outline it using a stylus. Participants were allowed to look at the simple shape for as long as they liked before they turned over to view the complex shape; they were also allowed to turn back to the simple shape as many times as they liked. Twelve items were presented in total and the time taken until the completion of each item was recorded with a maximum of three minutes allowed for any single item.
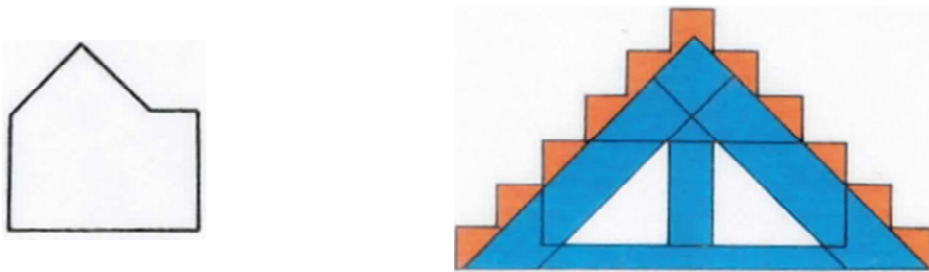
Figure 4.3: Example of simple shape and complex design from EFT

4.2.2.3: Social cognition

Two social cognition tasks were used: an emotion recognition task and a mentalising task.

Emotion recognition

The emotion recognition task was the presentation of the standard Ekman 60 faces (Ekman, Friesen et al. 1975) (Figure 4.3). Each face was presented for a maximum of five seconds and participants were asked to select what emotion the face was showing from a list presented in a random of order of fear, anger, disgust, sadness, happiness and surprise. Ten presentations of each of the 6 emotions were presented in a random order.

Performance for each emotion was measured separately and a combined total was also generated.
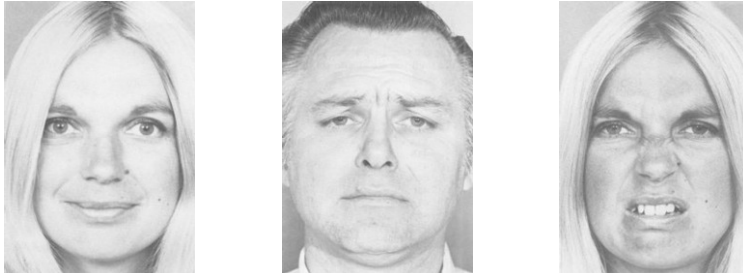
Figure 4.4: Sample stimuli from the Ekman faces showing happiness, sadness and disgust

Mentalising

The mentalising task employed was the Social Judgements Task (Hall, Harris et al. 2004). Participants were shown six sets of forty pictures of faces (eight practice and thirty two scored images) for a maximum of five seconds each. In each set they were asked to allocate the faces into one of the following binary characteristics: approachable-unapproachable, distinctive-not distinctive, young-old, trustworthy-untrustworthy, intelligent-not intelligent and attractive-unattractive. The pictures were shown on a computer screen and the participants pressed a button on a keyboard to indicate their selection. No feedback was provided as to their responses.

The stimuli for this test were the same as those derived for a previous study (Hall, Harris et al. 2004). Briefly, five hundred pictures of non-famous faces were evaluated by six volunteers across the six dimensions above using ratings between 0 and 7. Twenty

pictures with opposite mean valences for each judgement were selected for each set of the final test materials. This meant that each test set consisted of forty pictures, 20 of one valence and 20 of the opposite (e.g. 20 attractive and 20 unattractive faces). Individuals in the current study were thus scored according to their agreement with the previously derived ratings. A total score for each judgement was recorded, as well as the direction of error (e.g. trustworthy faces rated as untrustworthy or vice versa).

4.2.3: Statistical analysis

Differences between the groups were examined using ANOVAs or repeated measures ANOVAs with follow-up t tests as appropriate when the data were parametric in distribution. For non-parametric data Kruskal-Wallis tests and follow-up Mann-Whitney tests were employed. Within the tables parametric data are presented as mean (standard deviation) whereas non-parametric data are presented as median (inter-quartile range). To assess the effect of IQ it was added as a covariate in an ANCOVA for parametric data; when one or more of the groups contained non-parametric data the effect of IQ was determined using partial correlations across all 4 groups, controlling for group. The relationships between continuous measures were determined using Pearson's correlation coefficient for parametric data and Spearman's rho for non-parametric data.

4.3: RESULTS

4.3.1: Participants

The characteristics of the participants are given in Table 4.1.

	ASD	SPD	CM	Controls
N	28	20	9	33
M:F	22:6	14:6	6:3	23:10
Age	39.5 (11.6)	37.3 (9.4)	35.8 (10.0)	36.5 (9.3)
Handedness	27:1	18:2	7:2	31:2
Yrs education	16.2 (1.7)	15.4 (2.0)	16.1 (2.4)	16.5 (1.9)
Verbal IQ	108.4 (14.0)	104.7 (11.9)	98.6 (23.7)	113.2 (9.8)
Performance IQ	114.6 (17.8)	106.7 (11.4)	105.3 (21.7)	119.1 (10.2)
Full-scale IQ	113.1 (17.3)	106.4 (10.7)	102.4 (23.6)	118.1 (9.9)
ADOS comm	3 (2)	1 (2)	2 (1)	0 (0)
ADOS SI	5 (1)	2 (2)	5 (3)	0 (0)
SPD items	2 (2)	5 (1)	5 (2)	0 (0)

Table 4.1: Characteristics of participants for neuropsychological experiment

No significant differences were seen between the groups with respect to gender (chi sq = 1.4, p= 0.70), handedness (Fishers exact test = 3.28, p=0.28), age (F=0.42, p=0.74) or years spent in education (F=1.27, p =0.29). IQ scores differed significantly between the groups (F=3.50, p=0.02; F=3.98, p=0.01; F=4.25, p=0.008 for verbal, performance and full-scale IQ respectively). In particular the control group had significantly higher IQ scores in all three domains than either the SPD or the CM group (all p<0.05). The ASD, SPD and CM groups did not differ significantly on any of the IQ measures, although there were trends towards significance for differences between the ASD and CM groups in verbal and full-scale IQ (all p>0.06).

4.3.2: Executive function

Sustained Attention and Inhibition

The median and interquartile range for the number of omission and commission errors on the different versions of the SART are shown in Table 4.2. There were no significant differences between the groups on any of the measures (all p>0.30).

	ASD	*SPD*	*CM*	*Controls*
Fixed				
Om Err	1 (4.0)	1.0 (6.5)	2 (4)	1 (2)
Comm Err	1 (3)	2.5 (3.5)	2 (1)	2 (2)
Random				
Om Err	0 (1)	0 (2.5)	1 (2)	0 (2)
Comm Err	3 (4)	4.5 (8.5)	7 (3)	4 (6)

Table 4.2: Results for Fixed and Random SART given as median (IQR).

Working Memory

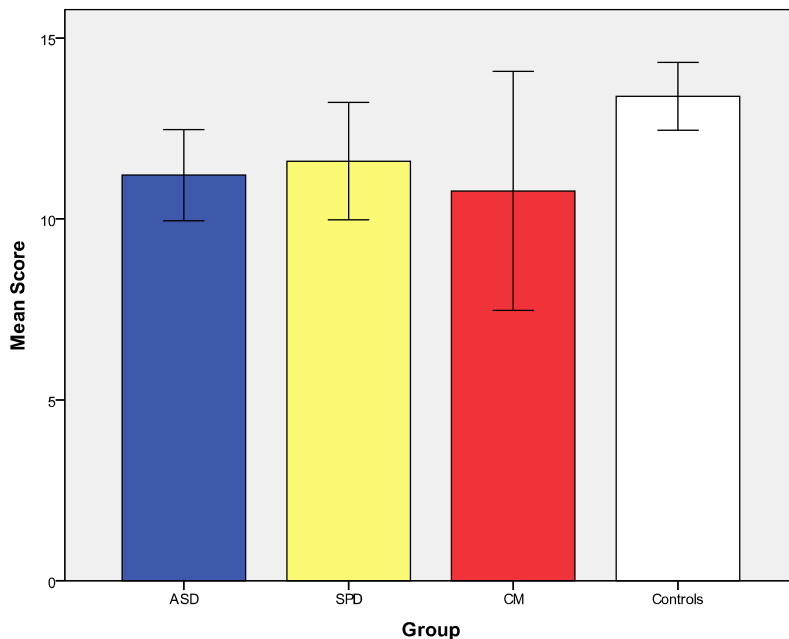The results for the letter-number sequencing task are shown in Table 4.3.

	ASD	*SPD*	*CM*	*Controls*
Level reached	4.0 (1.0)	5.0 (2.0)	4.0 (1.0)	6.0 (2.0)
Total score	11.2 (3.2)	11.6 (3.5)	10.8 (4.3)	13.4 (2.6)

Table 4.3: Results for letter-number sequencing task

For level reached results are given as median (interquartile range). For total score results are given as mean (standard deviation).

Significant differences were found between the groups for the level reached (chi sq = 15.7, p=0.001) and for the total score (F=3.17, p=0.03) (Figure 4.5). In terms of the level reached, the controls scored more highly than the ASD and CM group (Z=-3.4, p=0.001; Z=-2.9, p=0.003 respectively but not the SPD group (Z=-1.6, p=0.10). There were no significant differences when the ASD group was compared to either the SPD or CM group (Z=-1.5, p=0.14 and Z=-0.77, p=0.44); however a trend towards significance was apparent when the SPD and CM groups were compared (Z=-1.7, p=0.08).

For the total score the controls scored significantly more highly than the ASD and CM groups (p=0.01 and p=0.03 respectively) and there was a trend towards significance for the control-SPD comparison (p=0.053). There were no significant differences between the ASD, SPD and CM groups (Figure 4.5)

Figure 4.5: Bar chart showing mean total score and 95% CIs for the letter-number sequencing task

When full-scale IQ was added as a covariate to the analysis the control-ASD comparison remained significant (p=0.03) while the control-SPD and the control-CM comparisons became non-significant (p=0.63 and p=0.50 respectively) (adjusted mean values: ASD=11.1, SPD=12.5, CM=11.8, Controls=12.7).

Generativity

The results of the FAS test are given in table 4.4.

	ASD	*SPD*	*CM*	*Controls*
Produced	13.8 (5.0)	13.0 (4.4)	13.4 (2.9)	16.3 (4.0)
Category rel	0.19 (0.12)	0.18 (0.14)	0.19 (0.14)	0.21 (0.11)
Phoneme rel	0.36 (0.16)	0.34 (0.14)	0.30 (0.12)	0.38 (0.19)

Table 4.4: Mean (standard deviation) performances on the FAS test.
Produced – total number of appropriate responses; category rel – total number of consecutive responses in same category / total appropriate responses; phoneme rel – total number of consecutive responses beginning with the same phoneme / total appropriate responses

The controls produced a greater mean number of responses per letter than the three other groups (F=3.26, p=0.03, 0.007 and 0.08 for the ASD, SPD and CM groups respectively). No other significant differences were found. When full-scale IQ was added as a covariate to the analysis the control-ASD comparison showed only a trend towards significance (p=0.07) while the control-SPD and the control-CM comparisons became non-significant (p=0.13 and p=0.68 respectively).

The results for the use of objects test are given in Table 4.5.

	ASD	*SPD*	*CM*	*Controls*
Total approp.	7.0 (3.2)	6.4 (3.0)	7.1 (3.0)	10.0 (4.0)
HI/approp.	0.03 (0.04)	0.00 (0.03)	0.00 (0.00)	0.00 (0.01)
Pers./total	0.01 (0.02)	0.00 (0.03)	0.00 (0.01)	0.00 (0.02)
Inapprop./total	0.10 (0.15)	0.12 (0.14)	0.13 (0.14)	0.12 (0.07)

Table 4.5: Mean scores per category for use of objects task.

Total approp. – appropriate responses, mean (sd); HI/approp. – proportion of appropriate responses considered to be highly imaginative, median (inter-quartile range); Pers./total – proportion of all responses which were perseverative, median (inter-quartile range); Inapprop./total – proportion of all responses which were inappropriate, median (inter-quartile range)

A significant main effect of group was seen for the number of appropriate responses per category (F=6.1, p=0.001). Controls scored more highly than each of the other three groups (all p<0.03). There were no significant differences between the ASD, SPD and CM groups. When IQ was added as a covariate the difference between the CM and control groups became non-significant whereas the other results did not change.

A significant difference between the groups was seen for the proportion of highly imaginative responses produced (chi sq = 9.8, p=0.02). The ASD group scored significantly more than the controls and the CM groups (Z=-2.6, p=0.009; Z=-2.2, p=0.03 respectively) and there was a trend towards a significantly higher score compared to the SPD group (Z=-1.69, p=0.09). No significant differences were seen between the other groups for the number of highly imaginative responses.

There were no significant differences between the groups with respect to the proportion of responses which were perseverative or inappropriate (chi sq = 3.5, p=0.31; chi sq=1.40, p=0.71).

4.3.3: Central coherence

Block design

There was no significant main effects for the ANOVAs comparing the groups on their performance on the unsegmented format of the block design task (F=2.02, p=0.12) whereas there was a trend towards a significant difference on the segmented format (F-2.20, p=0.09). Broadly speaking the controls performed the task more quickly than the SPD or CM groups regardless of format (see figure 4.5) with the ASD group falling in between the two. Because performance on block design forms a significant component of full-scale IQ, the moderating effect of differing intellectual ability was examined by including verbal IQ as a covariate. This led to all the results becoming non-significant (F=0.17, p=0.92). Thus we did not see the anticipated superior performance of individuals with ASD on the block design task.

In order to assess whether there were differences between the groups with respect to the facilitation provided by the provision of segmented designs, a repeated measures ANOVA was conducted with the within subject variables as mean time taken to solve the each item in its segmented and unsegmented forms and group as a factor. Although there

was some evidence that the ASD group showed the least facilitation, no significant group x task form interaction was observed (F= 1.2, p=0.33; figure 4.6) and this did not change with the addition of verbal IQ as a covariate.
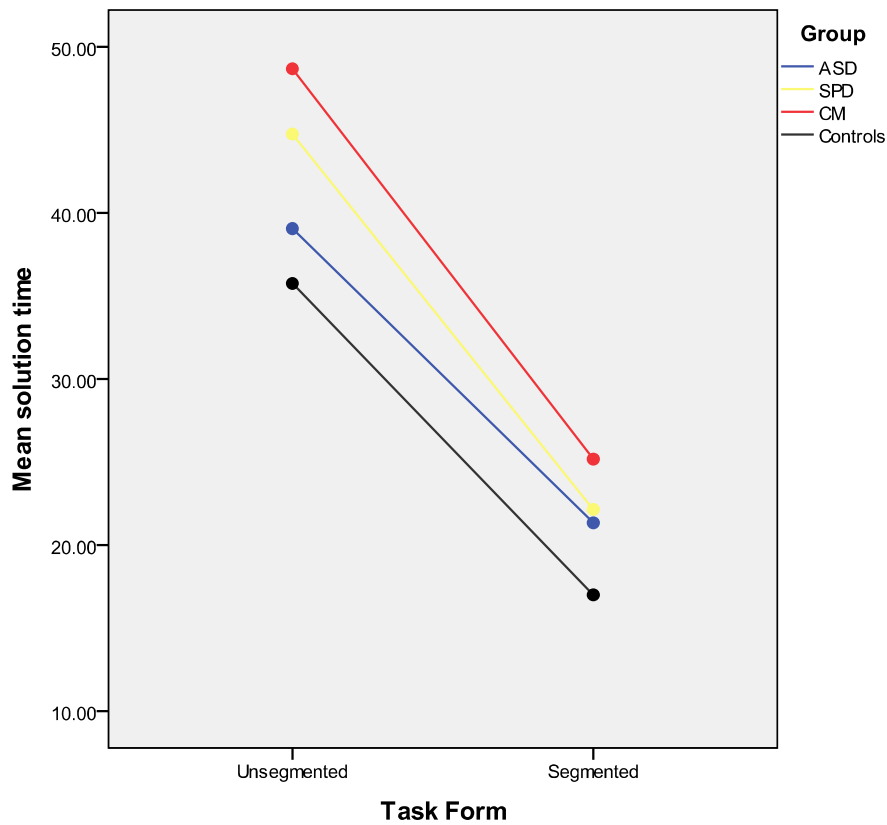

Figure 4.6: Performance on the segmented and unsegmented block design task

Embedded Figures Test

The Kruskal-Wallis test showed a significant difference between the groups with regard to the mean time taken to solve the items (chi sq = 8.95, p=0.03, figure 4.7) and there was a trend towards significance in terms of the number of items correctly solved (chi sq = 6.9, p=0.07). The follow-up Mann-Whitney tests showed that the SPD group took longer to solve the embedded figures than the controls and the ASD group (Z=-2.73, p=0.006,

Z=-2.22, p=0.03). Although the comorbid group took longer than any of the groups, none of these differences were significant (all p>0.10). Again the ASD group did not show the expected superior function relative to the controls.
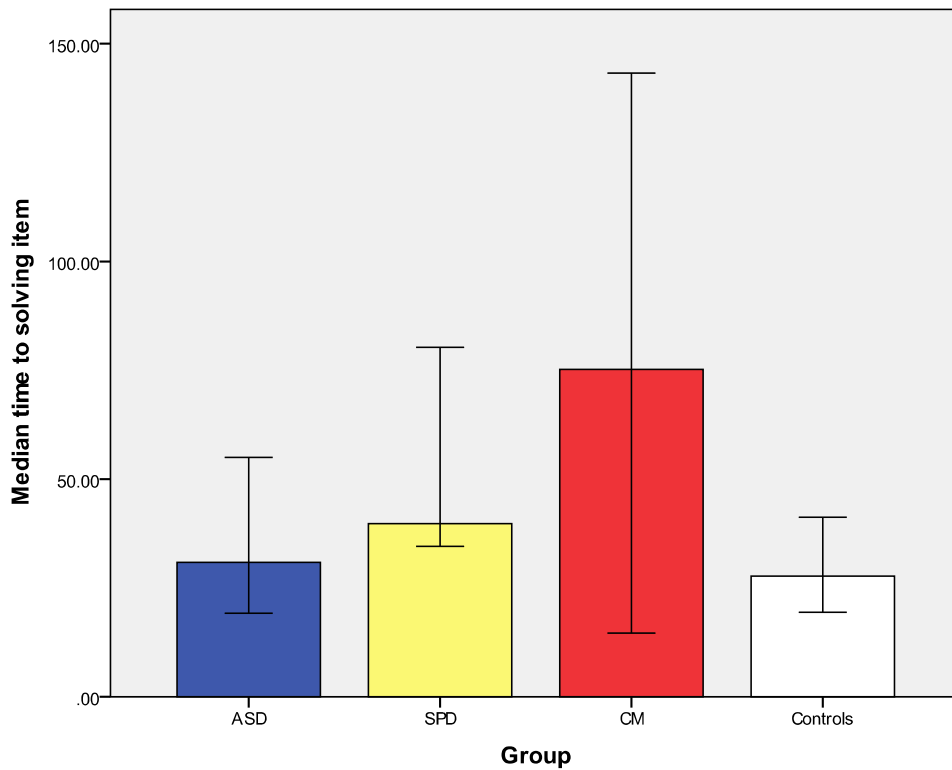
Figure 4.7: EFT performance shown as median time taken to solve item with 95% CIs

Strong correlations exited between IQ and performance on the EFT (r=-0.72, p<0.001 across all groups) suggesting that the differences reported may relate to IQ differences between the groups. There was some evidence that IQ accounted for a greater degree of the variance of the EFT scores in the ASD, CM and control groups than the SPD group (rho squared = 0.49, 0.84, 0.47 and 0.15 respectively).

Similar to the findings for IQ, there was a significant association between EFT and working memory performance in the ASD and CM group with a trend towards significance in the controls (rho=-0.69, p<0.001; rho=-0.70, p=0.04; and rho=-0.32, p=0.07) but not in the SPD group (rho=-0.22, p=0.34) (Figure 4.8)
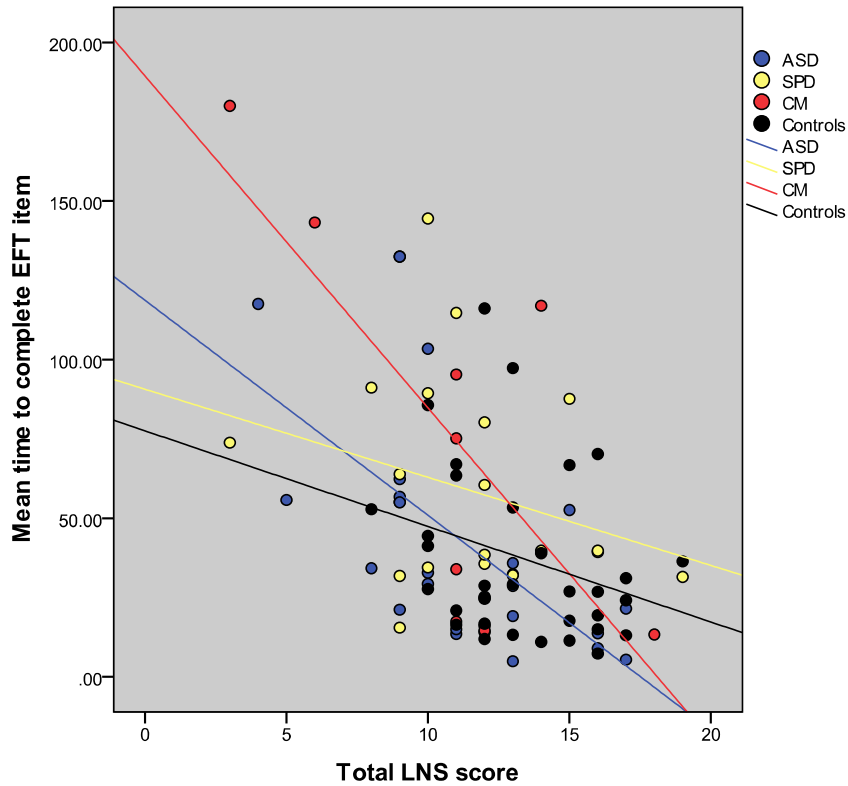
Figure 4.8: Relationship between working memory and EFT

4.3.4: Social cognition

Face Emotion Recognition

The scores for the Ekman 60 test are summarised in Table 4.6 and Figure 4.9.

	ASD	*SPD*	*CM*	*Controls*
Anger	8 (1.5)	8 (2)	8 (3)	9 (1)
Disgust	8 (4)	8 (2.5)	8 (2)	8 (2)
Fear	6.5 (4)	6 (3.5)	7 (4)	8 (2)
Happiness	10 (0)	10 (0)	10 (0)	10 (0)
Sadness	7 (3)	8 (2)	8 (2)	8 (2)
Surprise	8.5 (3)	9 (3)	9 (1)	9 (2)
Total	47 (8.5)	49 (9.5)	48 (10)	51 (4)

Table 4.6: Results of the Ekman60 face emotion recognition task. All given as median (inter-quartile range)

Significant differences between the groups were seen for anger, fear and the total score (chi sq=9.6, p=0.02; chi sq = 8.4, p=0.04 and chi sq=8.70, p=0.03 respectively). For anger, the ASD group scored significantly less than the controls and there was a trend towards a significant decrease in the CM group compared to the controls (Z=-3.14, p=0.002 and Z=-1.65, p=0.099 respectively). For fear the ASD, SPD and CM groups all scored significantly less than the controls (Z=-2.29, p=0.02; Z=-2.2, p=0.03; Z=-1.97, p=0.049 respectively). For the total score a significant reduction compared to controls was seen for the ASD group (Z=-2.94, p=0.03) and a trend towards a significant

reduction was seen for the CM group (Z=-1.74, p=0.08). No other significant differences or trends towards significant differences were seen.
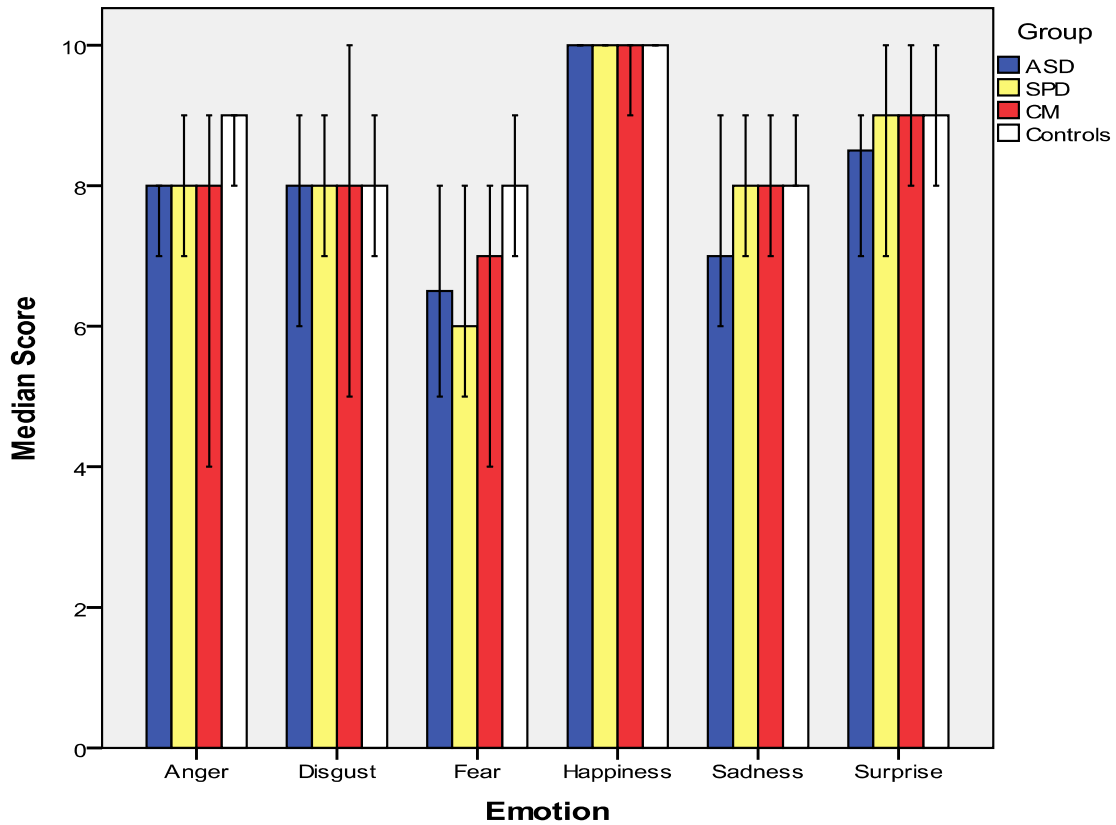
Figure 4.9: Ekman 60 results shown as median with 95% CIs

In order to assess whether IQ differences affected the results, partial correlations controlling for group membership were conducted between full scale IQ and the results for anger, fear and total Ekman60 scores. Significant positive relationships were seen for IQ with anger and the total score (both p<0.001) whereas no significant relationship was seen for fear (p=0.10). This suggests that the group differences for anger and the total score may relate to the IQ differences between the groups, but this is less likely for fear.

The results of the social judgements task are shown in Table 4.7 and Figure 4.10.

	ASD	*SPD*	*CM*	*Controls*
Age	31 (1.5)	31 (2)	30 (2)	31 (1)
Approachability	24.5 (8.5)	26 (8.5)	27 (9)	29 (5)
Attractiveness	26.5 (6.5)	26 (5)	28 (3)	29 (3)
Distinctiveness	23 (3.5)	22.5 (6.5)	21 (5)	25.5 (3.5)
Intelligence	26 (4)	27 (6.5)	28 (3)	28 (3)
Trustworthiness	25.5 (4)	23.5 (7)	24 (5)	25.5 (4)
Total	160 (18)	155 (19)	153 (22)	166 (11.5)

Table 4.7: Results of social judgement task given as median (IQR)

Significant differences between the groups were seen for judgements of attractiveness, distinctiveness and intelligence (chi sq = 9.9, p=0.02; chi sq= 11.9, p=0.008; chi sq= 8.0, p=0.046 respectively) and trends towards significant differences were seen for judgements of age and approachability (chi sq=7.2, p=0.07; chi sq=6.9, p=0.07 respectively). A significant difference between the groups was also seen for the total score (chi sq = 12.78, p=0.005).

Follow-up Mann Whitney tests showed that the ASD, SPD and CM groups did not differ significantly from each other on any of the measures (all p>0.13). The ASD group scored significantly less than the controls on the total score (Z=-2.73, p=0.006) and on

judgements of approachability, attractiveness, distinctiveness and intelligence (Z=-2.31, p=0.02; Z=-2.47, p=0.01, Z=-2.60, p=0.01; Z=-2.66, p=0.008 respectively) with a trend towards a significant difference for age (Z=-1.85, p=0.06). The SPD group scored less than the controls on the total score (Z=-3.09, p=0.002) and on judgements of approachability, attractiveness, distinctiveness and intelligence (Z=-2.04, p=0.04; Z=-2.69, p=0.007; Z=-2.30, p=0.02; Z=-1.97, p=0.046 respectively). The CM group scored significantly less than the controls on judgments of age and distinctiveness (Z=-2.39, p=0.02; Z=-2.64, p=0.008 respectively) with a trend towards a significant difference for attractiveness (Z=-1.75, p=0.08) and for the total score (Z=-1.96, p=0.051). No other significant differences were seen between the groups.
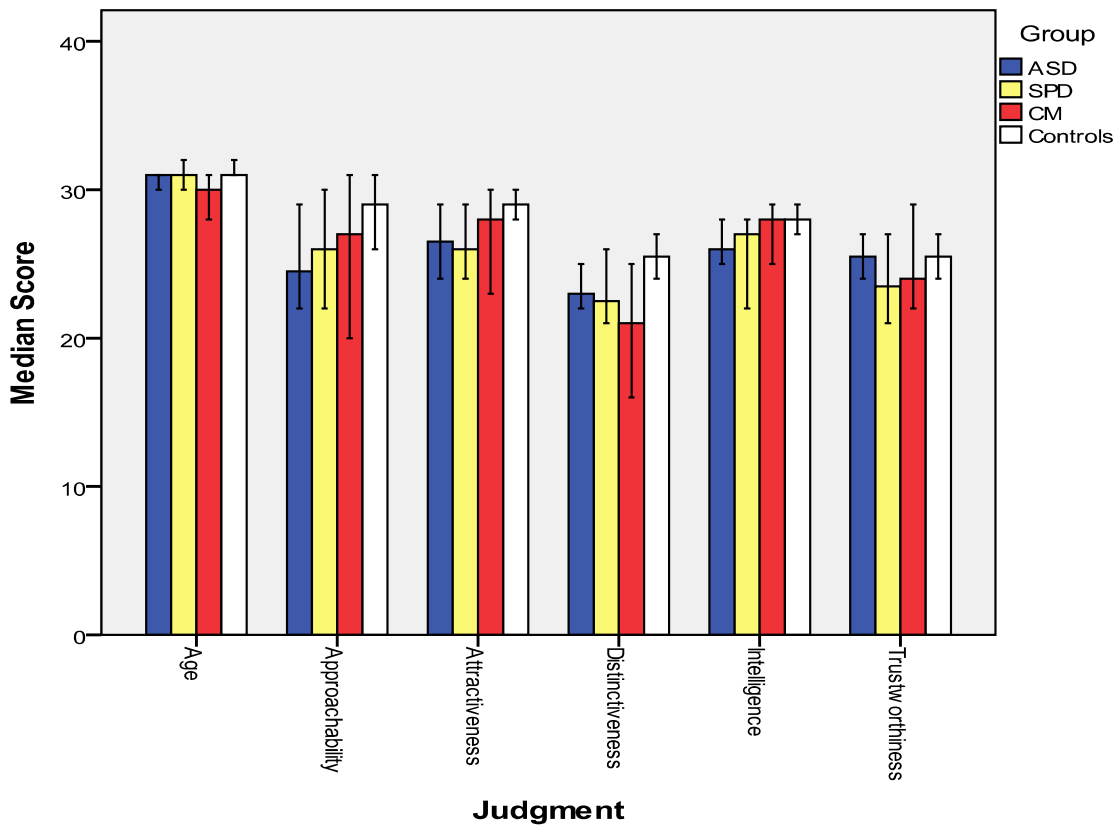

Figure 4.10: Scores on social judgement task given as median and 95% CI

To investigate whether the differences are confounded by IQ, partial correlations controlling for group between IQ and each measure were carried out. IQ had a significant effect on judgements of age, distinctiveness and on the total score suggesting that these results may relate at least in part to IQ differences between the groups.

For each measure the direction of error was also compared between the groups (i.e. whether one group was more likely to make approachable judgements from an unapproachable face or vice versa). No significant differences were identified between the groups with respect to the direction of the errors made in each judgement (all p>0.16).

Finally, whether the relationship between face emotion recognition and social judgement abilities differed between the groups was investigated by examining the correlations between the total scores for the Ekman faces test and the social judgement test. There was a significant group x emotion recognition score (F=3.88, p = 0.01); the ASD group showed a significant relationship between Ekman faces score and social judgement score (r=0.56, p=0.002) whereas the other groups did not (r=0.26, p=0.27 for SPD; r=0.47, p=0.20 for CM; r=-0.26, p=0.15 for controls) (see Figure 4.11).
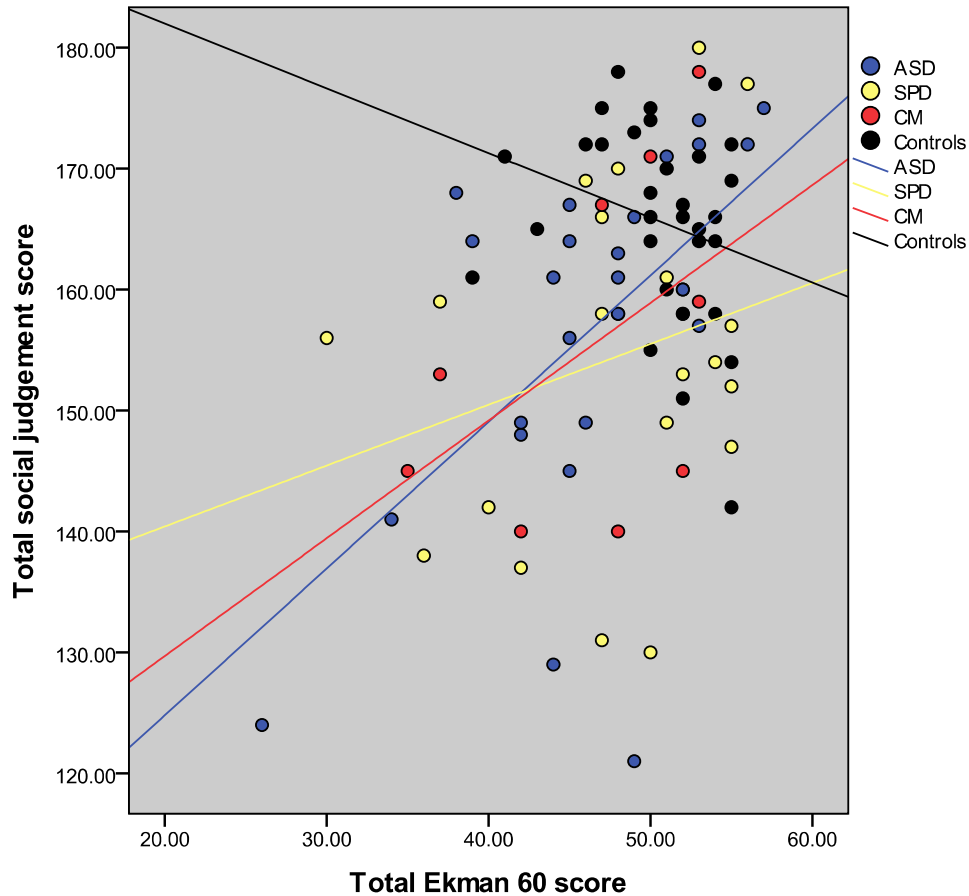
Figure 4.11: Correlations between total score on social judgment task and total score on Ekman 60 test in each of the four groups under study

4.3.5: Correlation of symptom domains with neuropsychological tests

Tests of interaction were performed to examine whether the groups differed with respect to the relationship between symptom domains (AQ, EQ, SIS positive, SIS negative and SIS disorganised) and the neuropsychological tasks which were found to be significantly different between the groups (FAS task; use of objects task; LNS task; EFT; social judgement task – approachability, intelligence, distinctiveness and attractiveness; and Ekman faces task – fear, anger).

A significant interaction was found between group and performance on the ideational fluency task with respect to the SIS positive symptom domain (p=0.046). Examination of the relationships within each group showed that the ASD, SPD and control groups all showed positive relationships between their scores on these measures (i.e. those with more positive symptoms tended to score more highly) whereas a negative relationship was seen in the CM group. However, none of these relationships were significant in themselves with the closest being a trend towards significance in the SPD group (r=0.40, p=0.09).

There was a significant interaction between the total score on the AQ and performance on the approachability subscale with a trend towards a significant interaction for the intelligence subscale of the social cognition task (p=0.02 and 0.07 respectively). No significant interaction was found for the non-mentalising judgements. When the groups were considered separately, the SPD group showed a significant negative relationship between AQ score and performance on the approachability task (rho=-0.47, p=0.04), the controls and the CM group both showed non-significant negative correlations, whereas the ASD group showed a non-significant positive correlation (Figure 4.12). A similar, but all non-significant, set of correlations was seen for the intelligence judgement.

Figure 4.12: Relationships between performance on the approachability task and the total AQ score.

4.3.6: Neuropsychological tests potentially confounded by IQ differences

A summary of the tests, on which IQ had a significant effect, and which may have accounted for differences between the groups is shown in Table 4.8. Only tests for which significant differences were seen between the groups are shown

Domain	Likely no effect of IQ	Potentially confounded by IQ
Executive Function	Use of objects task	Working memory Verbal fluency
Central Coherence		Embedded Figures Task
Social Cognition	Emotion recognition - fear Social judgement - approachability - attractiveness - intelligence	Emotion recognition - anger - total score Social judgement - age - distinctiveness - total score

Table 4.8: Neuropsychological tests for which significant differences between groups were seen which were potentially confounded by IQ

4.4: DISCUSSION

Using a battery of neuropsychological tests covering executive function, central coherence and social cognition, differences were identified between the controls and the clinical groups (ASD, SPD and CM) on several of the tests. This was particularly evident for social cognition, where deficits in performance were seen for all of the clinical groups, and to a lesser extent executive function, where deficits were seen but were almost entirely accounted for by IQ (Table 4.8). However, there were remarkably few differences apparent when the clinical groups were compared to each other, which is particularly striking given that the tests were specifically chosen with the intention of distinguishing between them.

Social cognition

Each of the ASD, SPD and CM groups showed impairments on the Ekman 60 test of facial emotion recognition, particularly with respect to fear. The ASD and CM groups also showed evidence of impairment with respect to anger and to the total score, although the significant effect of IQ on performance on these measures may mean that the CM-control difference in particular is artefactual. These findings are broadly consistent with the hypothesis derived from the literature review in Chapter 2 that emotion recognition deficits would be apparent in all groups, and may be more marked in those with ASD (although no significant difference between the ASD, CM and SPD groups were seen).

The Ekman 60 is a comparatively simple emotion recognition task in that it consists of stationary stimuli with archetypal emotional expressions. Previous studies have suggested that deficits are more recognisable with more complex stimuli (Harms, Martin et al. 2010) therefore the current findings are strongly suggestive that these groups show genuine and marked deficits in emotion recognition.

The findings for fear are particularly striking across all three groups and may relate to a number of different reasons. Firstly the recognition of fear is generally held to be more complex than, for example, happiness or sadness, therefore the deficits reported here may be an effect of task difficulty. Secondly, it is well established that the amygdala has a prominent role in judgements of fear (Fusar-Poli, Placentino et al. 2009), and amygdala dysfunction has been suggested as to play a key role in the pathogenesis of both autism and schizophrenia spectrum disorders (Baron-Cohen, Ring et al. 2000; Hall, Whalley et

al. 2008). Interestingly, there was some evidence that the ASD and CM groups were additionally impaired at the recognition of anger, which has been associated with the insula (Fusar-Poli, Placentino et al. 2009), suggesting that a potentially broader impairment in social brain function occurs in these conditions.

The deficits in social judgements across the clinical groups were striking in their similarity across the groups, particularly between the ASD and SPD groups. Impairments in judgements of approachability, intelligence, attractiveness and distinctiveness were apparent in both the ASD and SPD groups, whereas neither showed impairments the detection of age or trustworthiness. Although all of these judgements are socially mediated, intelligence, approachability and trustworthiness likely require a greater degree of mentalising ability than attractiveness, distinctiveness or age. Thus the deficits reported here may not be specific for mentalising decisions per se but may be more broadly related to the ability to make social judgements, or possibly be due to a combination of mentalising deficits and sociocultural factors which affect how one judges attractiveness and distinctiveness.

The lack of a significant difference on the trustworthiness task was contrary to the hypothesis of worse performance by the SPD group due to the over-ascription of untrustworthiness. It is possible that this may relate to selection bias as over-ascription of untrustworthiness has been specifically associated with the presence of paranoid features (Couture, Penn et al. 2010) and it is possible that it is the less paranoid individuals with

SPD who were willing to undergo the detailed interviews, cognitive testing and MRI scanning required for the current study.

Interestingly a significant difference was found between the groups with regard to the relationship between performance on the emotion recognition task and on the social judgement task, such that the ASD group showed a significant positive association which was not seen in the other groups. The greatest difference was seen between the ASD and control groups with the SPD group in between the two and the CM group performing similarly to the ASD group. The positive association in the ASD group (and possibly also the CM group) suggests that these individuals may make social judgements based upon the same strategy by which they recognise emotions, whereas the control group do not. If, as suggested (Tantam, Monaghan et al. 1989; Gross 2008), individuals with ASD use local, feature based processing to recognise emotions, it is possible that they use similar explicit techniques to make a social judgement, whereas controls use more implicit processing, with people with SPD employing a mixture of the two.

There was some evidence also of a difference between the groups with respect to the relationship between autistic traits and performance on the approachability task. The significantly negative relationship between these measures in the SPD group contrasts with the lack of a relationship found in the other groups and suggests that mentalising dysfunction is more closely associated with clinically expressed autistic traits in the SPD group than in the other groups.

Executive Function

No difference in sustained attention or inhibition were seen between any of the groups. This is in contrast to previous studies in schizophrenia which have shown impairments in both domains, and to a lesser extent studies in SPD, where increased omission and commission errors have been reported in the Continuous Performance Test in individuals with SPD (Siever and Davis 2004) and general population samples with psychometrically defined schizotypy (Bergida and Lenzenweger 2006; Giakoumaki 2012). Impairments on the Random SART have been reported in individuals with psychometrically defined schizotypy, although only in terms of efficiency (a measure derived from the number of correct response divided by the average reaction time of correct responses); no significant differences were seen between the schizotypal individuals and controls in terms of commission or omission errors (Chan, Wang et al. 2009). It is possible therefore that the SART is not a sensitive enough measure of attention or response inhibition to capture the deficits in SPD which are more subtle than in schizophrenia.

Differences between the groups were apparent for working memory, measured using the letter-number sequencing (LNS) task, such that the clinical groups all scored less than the controls. After IQ was taken into account the difference was still apparent for the ASD group, but not for the SPD or the CM group who now scored midway between the ASD group and the controls. No differences between the ASD, SPD and CM groups were apparent either with or without IQ as a covariate. This is in contrast to the hypothesis that individuals with SPD would perform less well than those with ASD who were expected to perform similarly to controls, due to their recruitment of compensatory

visuospatial networks. However, this hypothesis was based primarily on findings of compensatory activity in people with ASD using functional MRI during the n-back task, which is a visually presented task. In contrast, the LNS is not visually based and as such may not be amenable to compensation by visuospatial regions. The current findings are therefore consistent with a theory of hypofrontality in ASD but not clearly so in SPD or CM individuals. One possible explanation is that SPD is not associated with prefrontal deficits. Alternatively, the compensatory increases in brain activity in prefrontal and other regions which have been reported to occur in schizophrenia (Glahn, Ragland et al. 2005) and in SPD (Koenigsberg, Buchsbaum et al. 2005), are acting in such a way to minimise the deficit in the current cohort. If this is the case this would imply that these compensatory mechanisms are different between ASD and SPD.

No evidence was found for enhanced generativity in SPD. Instead all three clinical groups performed less well than the control on the verbal fluency test. These differences became non-significant following the addition of IQ as a covariate, although there was still some evidence suggestive of a deficit in the SPD and, to a lesser extent, the ASD groups. The ASD, SPD and CM groups also showed reduced performance on the use of objects task compared to controls and this was robust to the addition of IQ. The reduced performance on verbal and ideational fluency in ASD is consistent with previous research (Turner 1999) and indicative of a general deficit in the ability to produce multiple novel responses to a general cue. In contrast to Turner et al (1999) the ASD group scored more highly than any of the other groups on the proportion of their responses considered to be particularly imaginative. This is not inconsistent with a generalised deficit in novelty

generation as it is the relative, but not total, number of highly imaginative responses that is increased. Rather it may reflect the 'autistic intelligence' suggested by Asperger (1991), which Wing felt was due to the lack of constraining sociocultural expectations constraints experienced by individuals with ASD (Wing 1981).

The lack of a performance advantage for individuals with SPD is contrary to findings of increased creativity in psychometric schizotypy (Nettle and Clegg 2006; Nelson and Rawlings 2010). However, it is consistent with the single study of verbal fluency in SPD which found reductions in performance compared to controls. The current study suggests that findings from general population studies of increased creativity associated with schizotypal traits do not generalise to a performance advantage for those with SPD. We did find evidence for non-significant positive relationships between ideational fluency and positive schizotypal traits within the ASD, SPD and control groups which suggests that the presence of such traits may be associated with increased creativity within each population, but that additional factors that differ between the populations may lead to the overall group differences reported in the current study. Raine (1991) reported that 55% of individuals in the top decile of scorers on the SPQ in a general population sample met criteria for SPD. Studies which have shown a creativity advantage in such samples may therefore be reflective of the relatively mild degree of schizotypy that they consider compared to the current study.

Central Coherence

In contrast to previous studies (Shah and Frith 1983; Shah and Frith 1993) and to the hypotheses of the current study, no advantage was seen for the ASD group compared to controls in tasks of weak central coherence. Although individuals with ASD showed the least facilitation from the segmented block design task, this did not come close to approaching significance, nor did they show overall superiority in the unsegmented block design task. Similarly, there was no evidence that the ASD group outperformed controls on the EFT. It is not clear why this should be; performance advantages on these tasks have been identified consistently in the past, indeed it has been the mechanism behind such advantages that is most debated, not whether they exist (Mottron, Burack et al. 2003; Happé and Booth 2008).

Although no evidence was seen for enhanced performance in the ASD group relative to controls there was some suggestion that individuals with SPD and CM individuals score less well than people with ASD on the EFT. Caution must be applied in interpreting this finding as there was a strong relationship between IQ and EFT performance suggesting that these differences might relate to differences in global intellectual ability. However, these findings are consistent with the work of Bolte et al who reported impaired performance in the EFT in schizophrenia compared to people with autism and controls and in parents of people with schizophrenia compared to parents of people with autism and controls (Bölte and Poustka 2006). It is unclear whether these deficits in EFT performance reflect poor local processing, enhanced global processing, a combination of

the two or a relative global processing bias regardless of the absolute local or global processing abilities.

What do the neuropsychological studies tell us about the relationship between the autism and schizophrenia spectrums?

The pattern of deficits in the CM group did not convincingly allocate them to any single diagnostic category (severe ASD, severe SPD) or a combination of categories. In part this may be due to the general lack of discrimination between ASD and SPD in the neuropsychological measures studied. There was some non-significant evidence that the CM group showed the same deficits as the SPD group on the EFT and use of objects task, but also showed the same deficits as the ASD group in terms of working memory. Thus, there is some suggestion that they may have the deficits of both the ASD and SPD group, providing some support for the combination or true comorbidity model. However, the lack of statistical significance means that these findings must be interpreted with caution. Interestingly, unlike the clinical studies, the CM group showed no evidence of being more affected from a neuropsychological perspective than the ASD and SPD groups.

Although several differences from controls were identified in the neuropsychological battery, remarkably few characteristics were found which discriminate between the ASD and SPD groups. Overall therefore the neuropsychological evidence suggests that ASD and SPD overlap considerably in terms of the cognitive function which underlies their clinical presentation. Certainly if differences between the groups are present they are subtle and it is possible that they may only be detected using precise instruments. There

was some evidence that working memory may be more affected in ASD than it is in SPD which may indicate a greater degree of prefrontal cortex impairment, or at least less effective compensatory mechanisms in the specific task that was used in the current study. Performance on the tests of social cognition were very similar between ASD and SPD, although there was also some evidence that the strategies used to make social judgements may differentiate them. The investigation of these domains using fMRI may provide useful insight into these issues.

Chapter 5

Experiment III

A functional magnetic resonance imaging comparison of ASD and SPD

5.1: INTRODUCTION

Functional MRI (fMRI) is a form of magnetic resonance imaging which is based upon two premises. Firstly, the brain does not store glucose. Instead when energy requirements in a specific region increase, for example due to increased neuronal activity, an increase in blood flow to that region is required. Secondly, oxygenated haemoglobin and deoxygenated haemoglobin have different magnetic properties and changes in their ratio therefore lead to a change in the signal detected during magnetic resonance imaging (Ogawa, Lee et al. 1990). This change in signal is called the blood oxygenation level dependent (BOLD) response. Therefore, by measuring the BOLD response, usually while an individual conducts different neuropsychological tasks, one is able to draw inferences about the relative blood flow to a particular brain region and hence relative neuronal activity.

It is important to note that the BOLD response is a proxy, rather than a direct measure of regional brain activity, and can be modulated by any variable that affects blood flow, not just neural activity. However, the lack of ionising radiation and good spatial resolution mean that fMRI is a valuable and popular tool for the *in vivo* study of human cognitive processes in health and in disease.

As reviewed in Chapter 2, fMRI has been regularly applied to the study of both schizophrenia spectrum and autism spectrum disorders. In the current study it is of particular interest because it may represent one way in which ASD and SPD can be better discriminated. fMRI has the potential to reveal whether the clinical and

neuropsychological similarities reported between ASD and SPD are associated with the same or different patterns of BOLD response, and hence allow inferences to be drawn about any relationship between the conditions.

Given that social deficits are one of the most strongly overlapping features between ASD and SPD, both from a clinical and a neuropsychological perspective, the need for their investigation using fMRI is clear. Both the ASD and SPD groups showed impairments on the approachability component of the social judgement task, but there was some evidence that they may differ in terms of its associations with emotion processing and clinically defined autistic traits. This indirect evidence that different brain mechanisms are associated with the mentalising deficit in ASD and SPD is consistent with the theories of hypo- and hyper-mentalising in autism and schizophrenia respectively (Abu-Akel and Bailey 2000; Frith 2004). If these theories are correct, predominantly underactivation of social brain regions should be seen in ASD while they make judgements of approachability, whereas predominantly overactivation should be seen in SPD while making the same judgements (although the caveats described in the opening paragraphs above should be noted). It was therefore hypothesised that individuals with ASD would show decreased activity of social brain regions than controls and that those with SPD would show greater activity in these regions compared to controls.

Verbal working memory was also found to be impaired in both the ASD and SPD groups, although this was not evident for the SPD group when IQ was taken into account. This was in contrast to previous findings which have suggested intact performance on the n-

back task of verbal working memory in people with ASD, despite evidence of reduced prefrontal activations, possibly due to the compensatory use of visuospatial regions (Koshino, Carpenter et al. 2005).Compensation has also been suggested to explain prefrontal and other hyperactivations which accompany prefrontal hypoactivation during the n-back task in schizophrenia (Glahn, Ragland et al. 2005) and SPD (Koenigsberg, Buchsbaum et al. 2005). By directly comparing BOLD response during the n-back task between participants with ASD and those with SPD it may be possible to not only determine whether frontal activation is similar between the disorders, but also whether compensatory activity occurs through increased activation elsewhere in the brain and whether the compensatory regions are the same or differ from each other. Based on the limited data available it was hypothesised that both groups would show reduced activation of the dorsolateral prefrontal cortex compared to controls and that this would not differ between them. It was also hypothesised that compensatory increases in activation would occur in visuospatial brain regions in ASD, whereas in SPD compensatory activations in prefrontal regions other than the dorsolateral prefrontal cortex would be seen. However, the working memory deficits identified in Chapter 4, particularly in the ASD group, suggest that the compensatory activity is not sufficient to maintain performance.

5.2: METHODS

5.2.1: Recruitment

Participants for this study were recruited from those who had completed the neuropsychological component outlined in Chapter 4. Two individuals (both from the ASD group) who completed the neuropsychological component did not take part in the imaging study due to their concerns about the scanner environment. A further two individuals (one control, one ASD) were excluded due to technical problems arising during their scans, such that meaningful data was not recorded. Finally, one individual with ASD was excluded due to the presence of a ferromagnetic earring causing significant artefact. The characteristics of the remaining participants are given in Table 5.1.

5.2.2: Image acquisition

All participants were scanned on a 1.5T GE Medical Systems Signa Scanner (GE Medical, USA). For the approachability task there were two experimental sessions, each acquiring 96 volumes. For the n-back task 210 volumes were acquired across one experimental session. For both tasks, axial, gradient-echo planar images (EPI) were acquired with a repetition time (TR) of 2.5s, echo time (TE) of 40ms, matrix 64 x 64, a field of view (FOV) of 240mm x 240mm and a flip angle of 90 degrees. Thirty contiguous 5mm slices were acquired in an interleaved fashion within each TR.

In addition to the functional acquisition, a T1 structural image was also obtained using an MPRAGE sequence. 180 contiguous 1.2mm thick coronal slices were obtained in an interleaved fashion (TR 9.7ms, TE 4.0ms, matrix 192 x 192, FOV 240mm x 240mm, flip angle 8 degrees).

5.2.3: Approachability task

The approachability task was applied as in Hall et al (2010). Participants were asked to decide whether people were approachable or not approachable, based upon pictures of their faces. As the control condition, participants were shown different face pictures and asked to decide if they were male or female. The face stimuli used were derived as described for the neuropsychological task in Chapter 4. No stimuli from the neuropsychological study in Chapter 4 were repeated in the imaging study, therefore, the stimuli employed were novel to all participants.

Stimuli were presented in blocks of approachability judgements ('social' condition) and gender judgements ('gender' condition). Two runs of the task were presented, each lasting 240 seconds. There were six blocks per run, three of the social conditions and three of the gender condition. Each block lasted for 25 seconds and blocks were separated by a baseline condition where participants were instructed to fixate on a cross in the centre of the screen ('Baseline' condition). Each block began with a 1 second visual reminder of the task for the block ("Approachable?" or "Gender?"). This was followed by 6 faces, in a pseudorandom order, each presented for 3.5 seconds with a 0.5 second gap between stimuli. Underneath the faces, participants were shown their

bivalent choice ("Approachable : Not approachable" or "Male : Female") and these were maintained on the screen throughout the block. They indicated their selection by pressing a button in the hand that corresponded to their choice.

Two pairs, A and B, each containing two forms of the task were created to permit counterbalancing of order and stimuli (four forms in total – A1, A2, B1, B2). Pair A began with the gender condition, whereas Pair B began with the social condition. In A1 and B1, participants were asked to make gender judgements on one set of stimuli and social judgements on another; this was then reversed for A2 and B2.

As per the out of scanner task in Chapter 4, performance was rated against the previously derived ratings for each picture derived in healthy controls (Hall, Harris et al. 2004).

5.2.4: N-back task

The stimuli for the n-back task were letters from the ISO basic Latin-script alphabet. Prior to each block written instructions were presented for 7.5 seconds as a cue to remind participants which condition this block contained. These were followed by the presentation of 12 stimuli, each for 1.5 seconds with a 1 second interval. In total the task lasted 525 seconds.

Four possible conditions were employed – 0-back, 1-back, 2-back and 3-back – with each block consisting entirely of only one condition. In all conditions, participants were asked to press a particular button every time they saw a letter, unless the letter was a target

stimulus in which case they would press a different button. The target stimulus varied between the four conditions. In the 0-back condition, the target stimulus was the letter 'X', thus the 0-back is considered a baseline condition with little working memory component. In the 1-, 2- and 3- back conditions the target stimulus was the letter shown one, two or three letters prior to the stimulus on the screen. Thus, these conditions are considered to place an increasing load on working memory. The number of correct responses for each condition were recorded as a measure of behavioural accuracy. The conditions were always presented in the order 0-back, 1-back, 2-back and 3-back, and this cycle was presented three times in total.

5.2.5: Image analysis

Image data were converted to NIfTI format and preprocessed using Statistical Parametric Mapping 8 software (SPM8 – www.fil.ion.ucl.ac.uk/spm/) running in MATLAB 2011b (The MathWorks, Inc). In each task the first four volumes of each run were discarded to avoid T1 equilibrium effects. This was followed by realignment to the mean EPI image to correct for small movements of the participants within the task. The functional images were then co-registered to the T1 structural image for each participant. Next, the T1 image was segmented and the parameters derived from this segmentation were used to normalise the T1 and the functional images to the standard Montreal Neurological Institute (MNI) template. The parameters from this were then used to normalise the functional images. Finally, the resultant functional images were then smoothed using an 8mm full width at half maximum Gaussian kernel.

Statistical analysis was conducted using the general linear model implemented in SPM8. For the approachability task, the data for individual participants were modelled with two explicit conditions (social judgement and gender judgement) and an implicit baseline. Parameters representing the participant's movement during the scan were also entered into the model as covariates of no interest. Contrast images were then generated for each participant for two contrasts: social versus baseline and gender versus baseline. In the second level analysis, a 2 x 4 flexible factorial design matrix was constructed with the two contrasts (social versus baseline and gender versus baseline) as within subjects factors and four groups (ASD, SPD, CM and control) as between-subjects factors in addition to the subject constants (Figure 5.1).
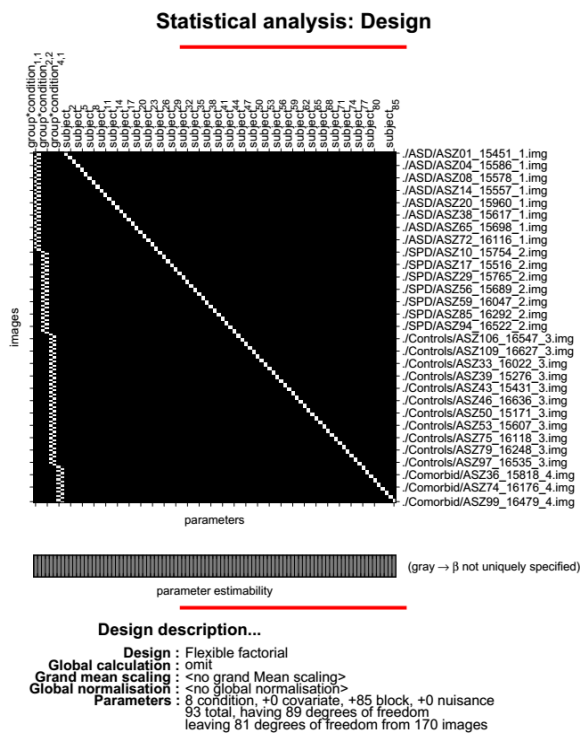
Figure 5.1: Design matrix for approachability task analysis

Using this design matrix contrasts were constructed to test: the main effect of condition (social or gender) across all four groups; the effect of condition within each group; and the group x condition interaction.

For the n-back task, the data for individual participants were modelled with four explicit conditions: 0-back, 1-back, 2-back and 3-back, and parameters representing the participant's movement during the scan were also entered into the model as covariates of no interest. Images were then generated for each participant for three contrasts: 1-back versus 0-back, 2-back versus 0-back and 3-back versus 0-back. In the second level analysis, a 3 x 4 flexible factorial design was constructed with the 3 contrasts as the within subjects factors and the 4 groups as the between subjects factor in addition to the subject constants (Figure 5.2).
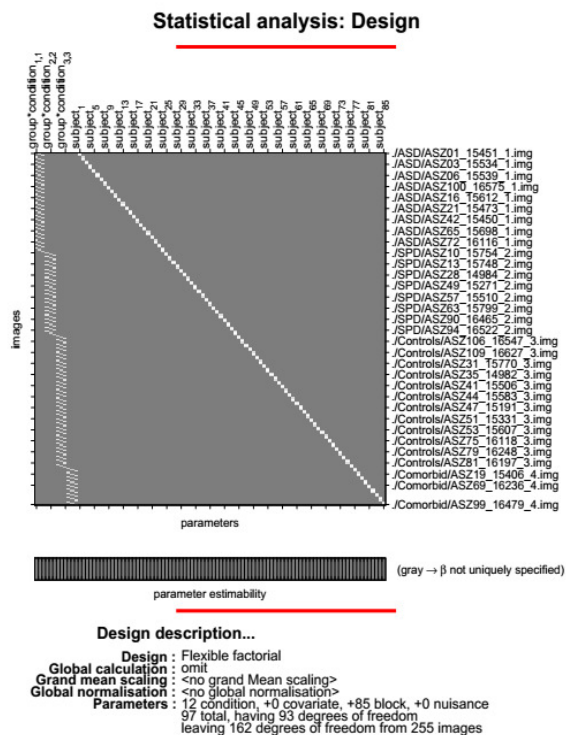
Figure 5.2: Design matrix for n-back task analysis

Using this design matrix the effect of interest was the change in activation as the n-back condition changed from 1-back to 3-back (i.e. as working memory load increased). As with the approachability task, contrasts were constructed to test: the main effect of condition across all four groups; the effect of condition within each group; and the group x condition interaction.

For the statistical maps from all analyses, other than those generated by the group x condition interactions, the height threshold was set at the level of p=0.001 uncorrected. Given that the group x condition interaction is a more subtle contrast, the height threshold was set at p=0.005 uncorrected. However, for all analyses results were only considered significant at p<0.05 after family wise error (FWE) correction for multiple comparisons across the whole brain.

In addition, for the approachability task, a small volume correction (SVC) was applied to the amygdala bilaterally. This SVC was derived through dilating the amygdala from the WFU-Pick Atlas toolbox for SPM by 1 voxel in order to ensure the whole structure was captured. Due to the small size of the amygdala, when SVC results are presented, the FWE corrected peak-level significance is given (as opposed to the cluster level significance). All significance values presented are therefore FWE corrected over the appropriate search volume (whole brain or SVC).

The anatomical regions corresponding to activated clusters were identified using the Anatomy toolbox plug-in for SPM8 (Eickhoff, Stephan et al. 2005) supplemented by the MNI atlas contained in the MANGO image viewer software package (http://www.nitrc.org/projects/mango/). Within the tables, the areas listed beside each cluster are all those contained within the cluster in the SPM output table which have a peak activation greater than the height threshold used.

For those clusters that showed a significant group x condition interaction, the eigenvariates for each cluster were extracted and the difference value calculated by subtracting the value for the gender condition from that for the social condition. This difference value was regressed against clinical variables of interest: positive, negative and disorganised traits as measured by the SIS and autistic traits as measured by the AQ and EQ. In addition, in order to assess the effect of potential confounding factors the difference values were also regressed against IQ and performance. These regression analyses were conducted within IBM SPSS Statistics for Windows, Version 19.0 (Armonk, NY: IBM Corp.).

5.3: RESULTS

5.3.1: Participant characteristics

The characteristics of the participants with valid imaging data are shown in Table 5.1.

	ASD	*SPD*	*CM*	*Controls*
N	24	20	9	32
M:F	19:5	14:6	6:3	22:10
Age	40.5 (11.9)	37.3 (9.4)	35.8 (10.0)	36.6 (9.5)
Handedness	23:1	18:2	7:2	30:2
Yrs. education	16.4 (1.6)	15.4 (2.0)	16.1 (2.4)	16.4 (2.0)
Verbal IQ	109.0 (14.1)	104.7 (11.9)	98.6 (23.7)	113.3 (9.9)
Performance IQ	115.4 (17.5)	106.7 (11.4)	105.3 (21.7)	118.8 (10.3)
Full-scale IQ	113.9 (17.1)	106.4 (10.7)	102.4 (23.6)	117.9 (10.0)
ADOS comm.	3 (1.5)	1 (2)	2 (1)	0 (0)
ADOS SI	5 (1)	2 (2)	5 (3)	0 (0)
SPD items	2 (2)	5 (1)	5 (2)	0 (0)

Table 5.1: Characteristics of participants who completed fMRI study

No significant differences were seen between the groups with respect to gender (chi sq = 0.94, p= 0.82), handedness (Fishers exact test = 1.10, p=0.35), age (F=0.72, p=0.55) or years spent in education (F=1.62, p =0.19). IQ scores differed significantly between the groups (F=3.48, p=0.02; F=3.93, p=0.01; F=4.25, p=0.008 for verbal, performance and full-scale IQ respectively). In particular the control group had significantly higher IQ

scores in all three domains than either the SPD or the CM group (all p<0.05). The ASD, SPD and CM groups did not differ significantly on any of the IQ measures (all p>0.05), although there were trends towards significance for differences between the ASD and CM groups in verbal and full-scale IQ (p=0.06 and 0.054 respectively).

5.3.2: Approachability task analysis

5.3.2.1: Performance

The scores for each group in the approachability judgement were: ASD – 27.8 (6.9); SPD – 27.4 (5.9); CM – 29.4 (4.8); controls 30.7 (4.7). Comparing the groups using ANOVA showed no overall main effect for a difference (F=1.92, p=0.13), although the follow-up comparisons did show evidence that the controls differed from the ASD and SPD groups (p=0.06 and p=0.04 respectively).

5.3.2.2: Main effect of condition

The main effect of condition shows the activation for the social versus gender contrasts when all four groups are considered together.

Significantly greater activation was found during the social > gender contrast bilaterally in the inferior frontal gyrus, superior medial prefrontal gyrus, insula, temporal poles, occipital regions and posterior cerebellum as well as in the left temporoparietal junction and right amygdala (Table 5.2 and Figure 5.3). No significant clusters were seen for the reverse contrast.

Regions in cluster	MNI of peak			Extent	P_{FWE}	Z_{peak}
Social > Gender						
L inferior frontal gyrus - p orbitalis and p triangularis L temporal pole L insula	-54	32	-2	218	0.01	3.99
R. inferior frontal gyrus - p triangularis R. temporal pole R. insula	51	29	-5	237	0.01	4.57
L. & R. superior medial gyrus L. & R. superior frontal gyrus	-9	-32	58	1121	<0.001	5.88
L. ant. inferior temporal gyrus L. medial temporal pole	-48	2	-35	146	0.048	5.11
L. post. middle temporal gyrus	-57	-43	1	346	0.002	4.43
L. & R. calcarine gyrus L. superior occipital gyrus L. lingual gyrus L. inferior occipital gyrus R. cerebellum - VI, VIIa Crus I & II	-9	-85	1	1953	<0.001	∞
L. cerebellum - VIIa Crus II	-39	-67	-44	245	0.009	5.74
R. amygdala	15	-4	14		0.01 [SVC]	3.52
Gender > Social						
No significant clusters						

Table 5.2: Brain activations during social versus gender contrast across all groups
Significance values reported are cluster values FWE-corrected for whole brain volume unless indicated using [SVC] when significance is reported for peak values FWE corrected for amygdala volume; L. = left; R. = right; ant. = anterior; post. = posterior
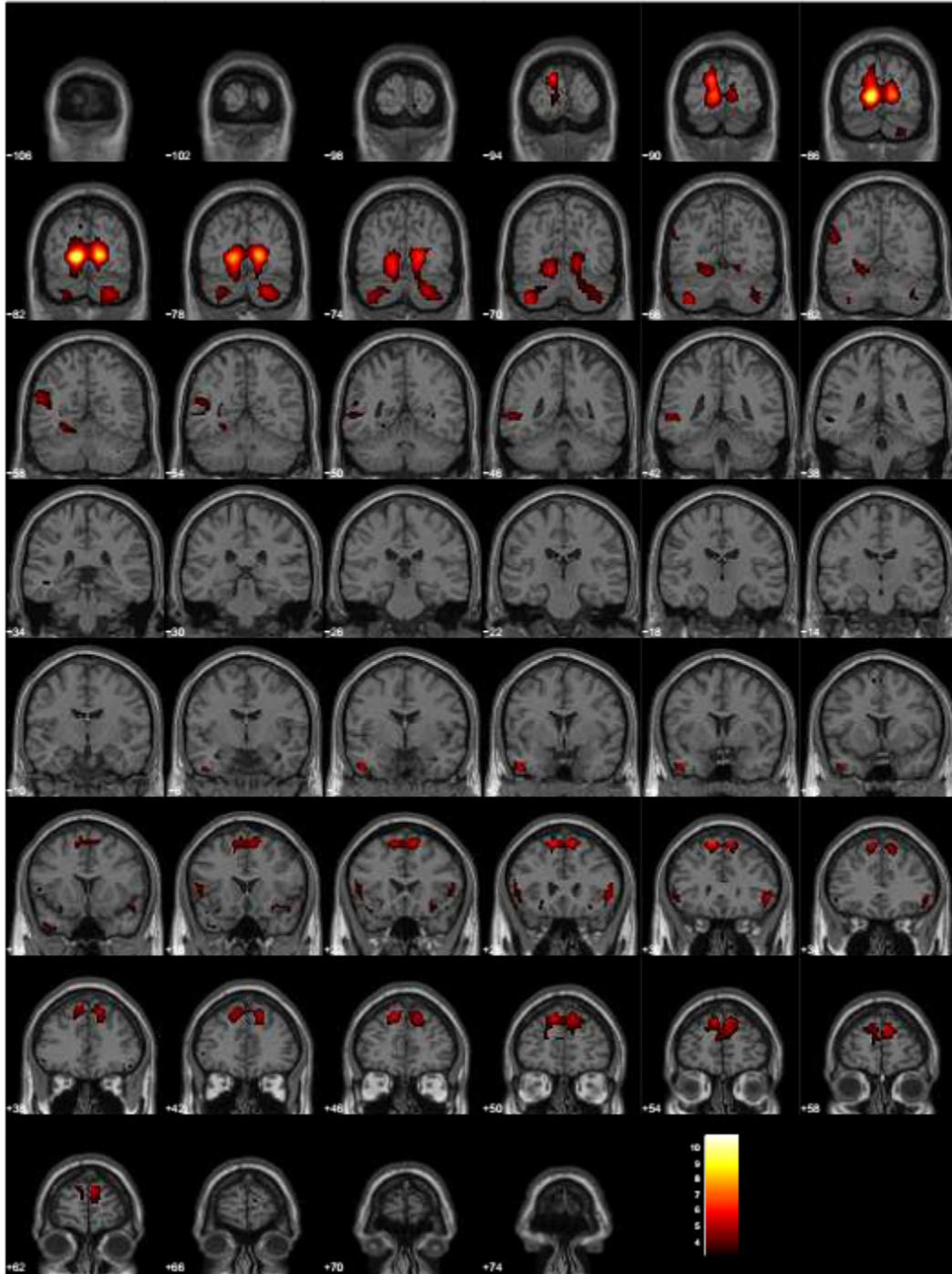
Figure 5.3: Clusters of activation for social > gender contrast across all four groups

Only clusters with a significance value of p<0.1 are displayed

No significant clusters were seen for gender > social

5.3.2.3: Brain activation within each group

Activations within each group for the social > gender and reverse contrasts are shown in Tables 5.3 – 5.5 and Figures 5.4 – 5.7.
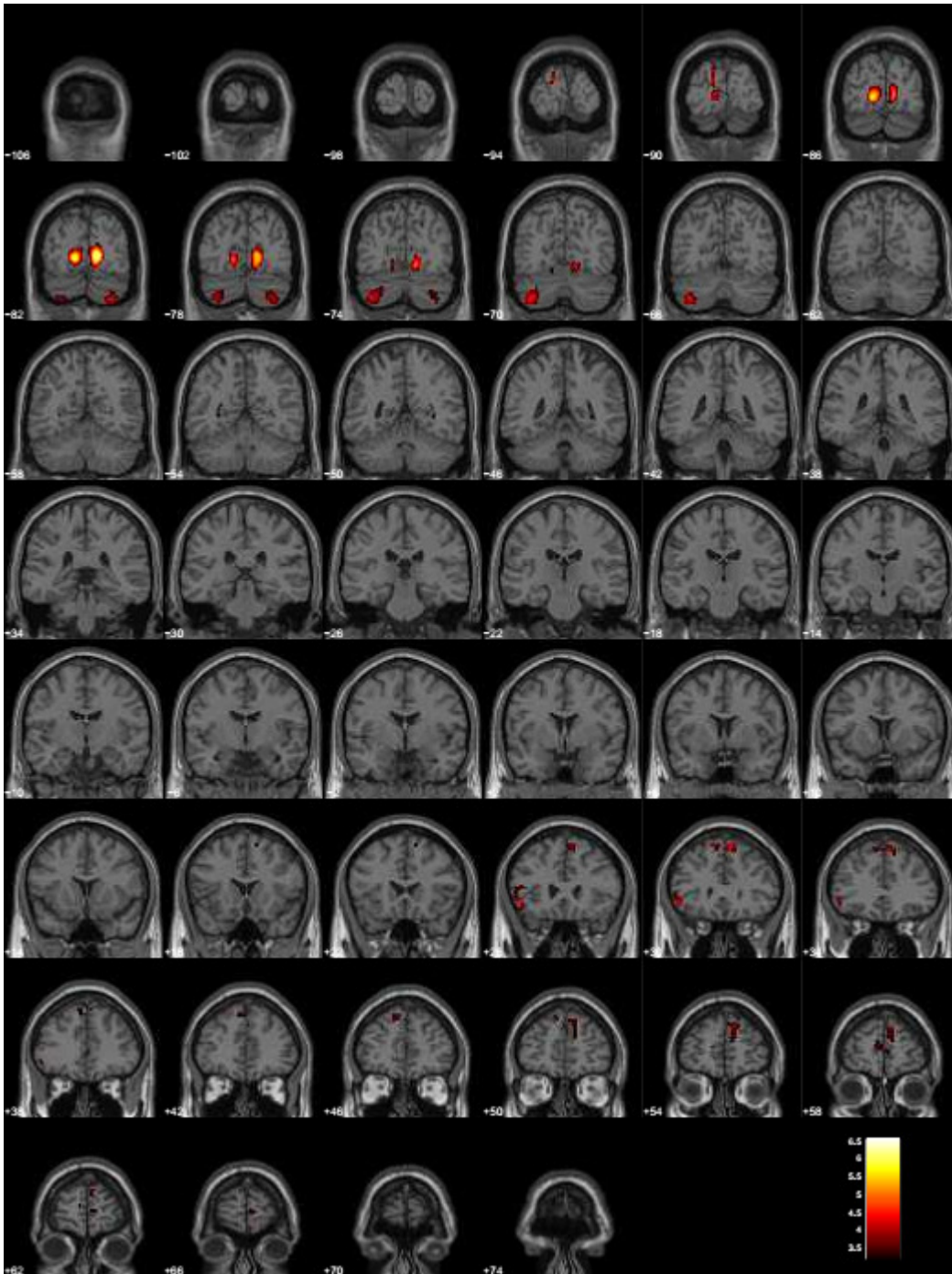
Within Controls

The controls showed significant areas of activation in the social > gender contrast in the right supplementary mot or area and the superior medial frontal lobe, occipital regions and the posterior cerebellum bilaterally. No significant activations were seen the reverse contrast (Table 5.3 and Figure 5.4).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Social > Gender						
L. & R. superior medial gyrus R. supplementary motor area	9	32	58	183	0.02	4.19
L. & R. superior medial gyrus	12	56	34	202	0.02	3.76
L. & R. lingual gyrus L. & R. superior occipital gyrus	12	-82	1	472	<0.001	5.86
L. cerebellum - VIIa Crus II	-36	-70	-44	201	0.02	4.24
R. cerebellum - VIIa Crus II)	30	-82	-44	114	0.09	3.97
Gender > Social						
No significant clusters						

Table 5.3: Brain activations during social versus gender contrast for control group

Figure 5.4: Activations within control group for social > gender contrast

Only clusters with a significance value of p<0.1 are displayed

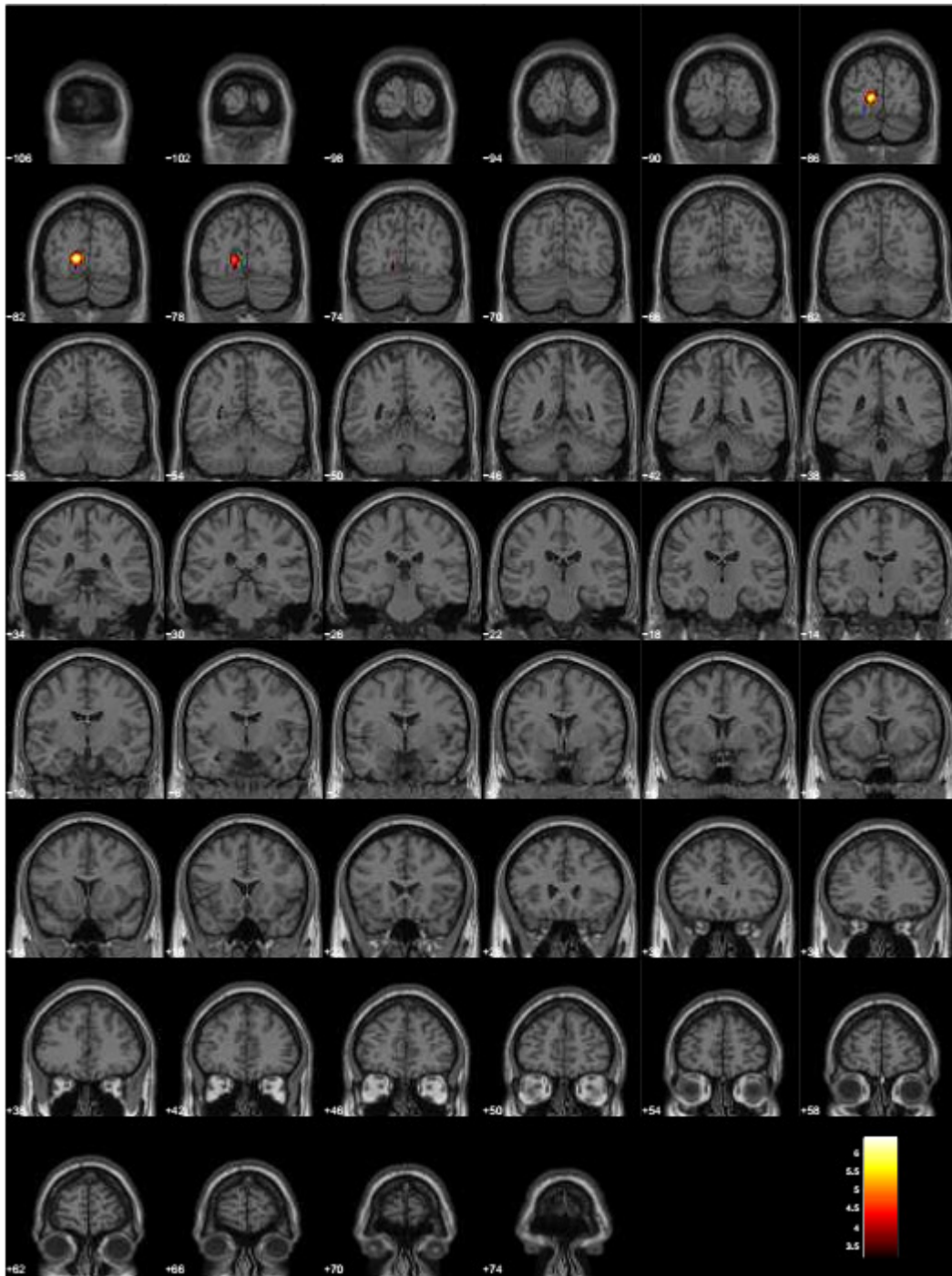No significant clusters were seen for gender > social

Within ASD group

The ASD group showed a trend towards significant activation in the left calcarine and lingual gyri during the social > gender contrast. No other areas of increased activation were seen in either of the contrasts (Table 5.4 and Figure 5.5).

Regions in cluster	MNI			Extent	P_{FWE}	Z_{peak}
Social > Gender						
L. calcarine gyrus	-9	-85	4	118	0.08	5.77
L. lingual gyrus						
Gender > Social						
No significant clusters						

Table 5.4: Brain activations during social versus gender contrast for ASD group

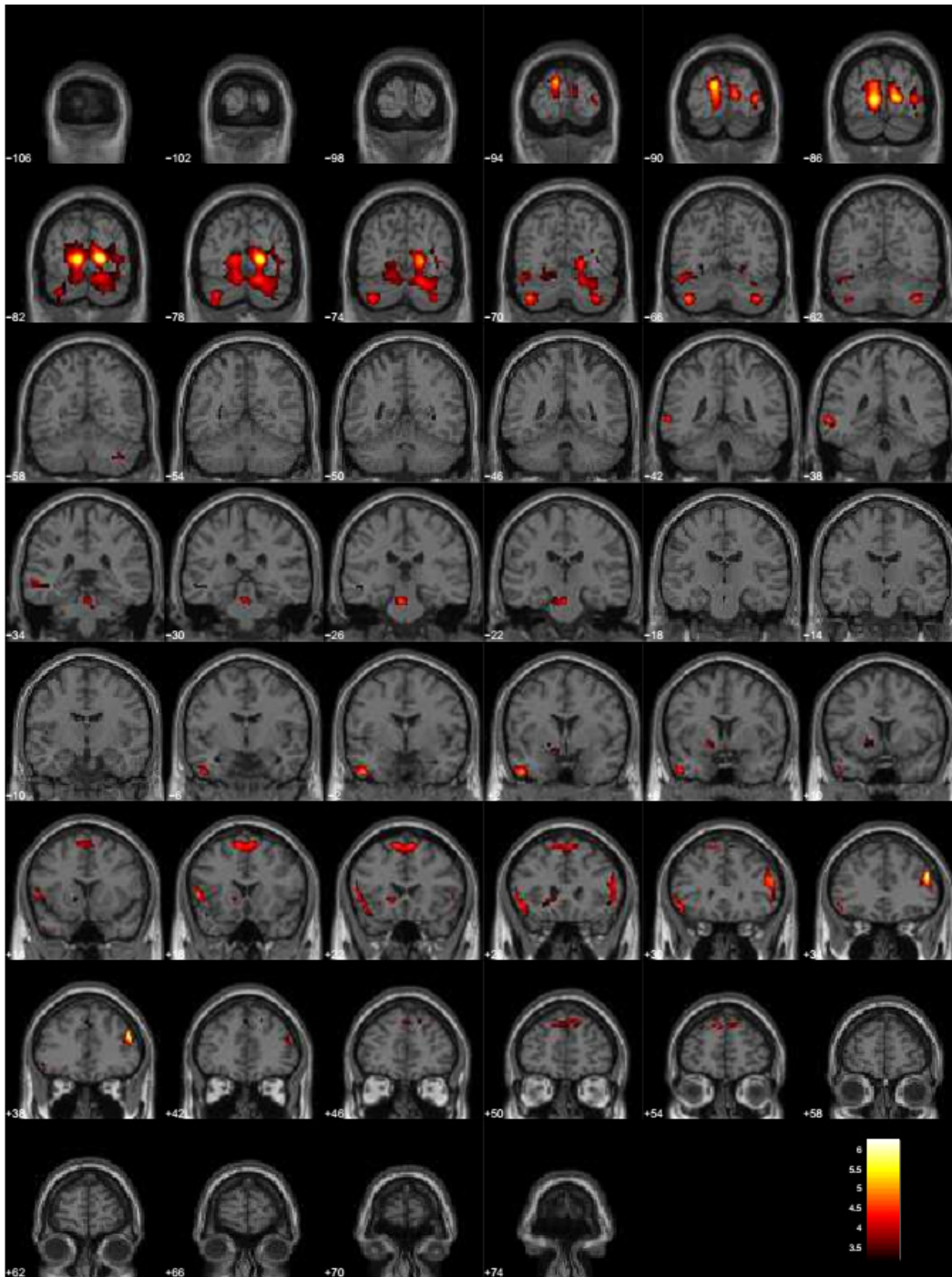**Figure 5.5:** Activations within ASD group for social > gender contrast

Only clusters with a significance value of p<0.1 are displayed

No significant clusters were seen for gender > social

Within SPD group

The SPD group showed significantly activated clusters in the social > gender contrast in the bilateral medial prefrontal cortex, inferior frontal gyri, medial temporal lobe and cerebellum, left temporal regions and basal ganglia (Table 5.5 and Figures 5.6 - 5.7).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Social > Gender						
L. superior frontal gyrus L. & R. supplementary motor area	-12	32	58	233	0.01	4.48
L. & R. superior medial gyrus R. middle cingulate cortex	-6	56	34	155	0.04	4.33
L. inferior frontal gyrus - p. orbitalis and p. triangularis	-54	17	4	200	0.02	4.6
R. inferior frontal gyrus - p. triangularis	51	35	25	232	0.01	5.52
L. inferior temporal gyrus L. temporal pole	-48	-1	-38	135	0.06	4.61
L. middle temporal gyrus	-63	-40	1	110	0.096	4.68
L. & R. calcarine gyrus L. superior occipital gyrus L. & R. Cerebellum - VI & VIIa Crus I and II	-9	-85	1	2422	<0.001	5.62
L. caudate & pallidum	-15	5	-5	136	0.058	3.86
L. hippocampus	-3	-25	-26	139	0.054	4.49
R. amygdala	15	-4	-14		0.02^{SVC}	3.38
Gender > Social						
No significant clusters						

Table 5.5: Brain activations during social versus gender contrast for SPD group

Figure 5.6: Activations within SPD group for social > gender contrast

Only clusters with a significance value of p<0.1 are displayed

No significant clusters were seen for gender > social
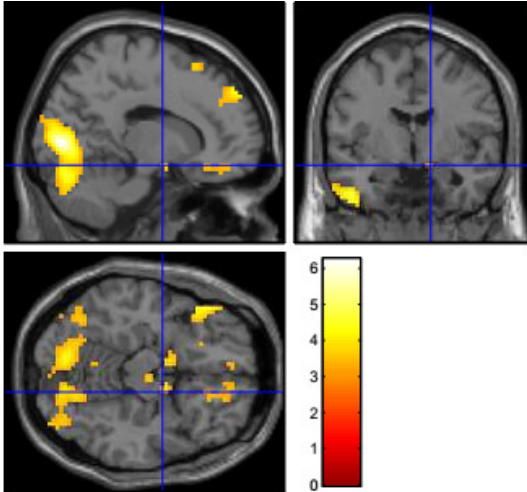
Figure 5.7: Location of right amygdala activation (MNI: 15 -4 -14) within SPD group for social > gender contrast

Within CM group

No significant regions of activation were seen in the CM group in either the social > gender or the gender > social contrast.

5.3.2.4: Group x condition interactions

The group x condition interaction provides an estimate of the difference between the groups with respect to the change in activation during the social decision compared to the gender decision. It thus represents an approximation of the activity associated with the purely social aspects of the task, as the non-specific visual and decision making elements are controlled for. As this contrast is more subtle than the previous ones, the initial height threshold was set as $p=0.005$ uncorrected. However, all significance values reported are FWE corrected for multiple comparisons. The results for the groups are given in Tables 5.6 to 5.9 and Figures 5.8 – 5.16.

Group x Condition Interaction: ASD versus Control

The ASD group showed significantly less activation than the control group in the posterior cerebellum bilaterally when making a social judgement as compared to a gender judgement (Table 5.6 and Figures 5.8 – 5.9). No areas were activated significantly more in the ASD group than the controls.

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
ASD > Control						
No significant clusters						
ASD < Control						
R. cerebellum - VI, VIIa Crus I and II	30	-58	-44	126	0.050	4.16
L. cerebellum - VI, VIIa Crus I and II	-45	-55	-41	329	0.07	3.52

Table 5.6: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and control groups
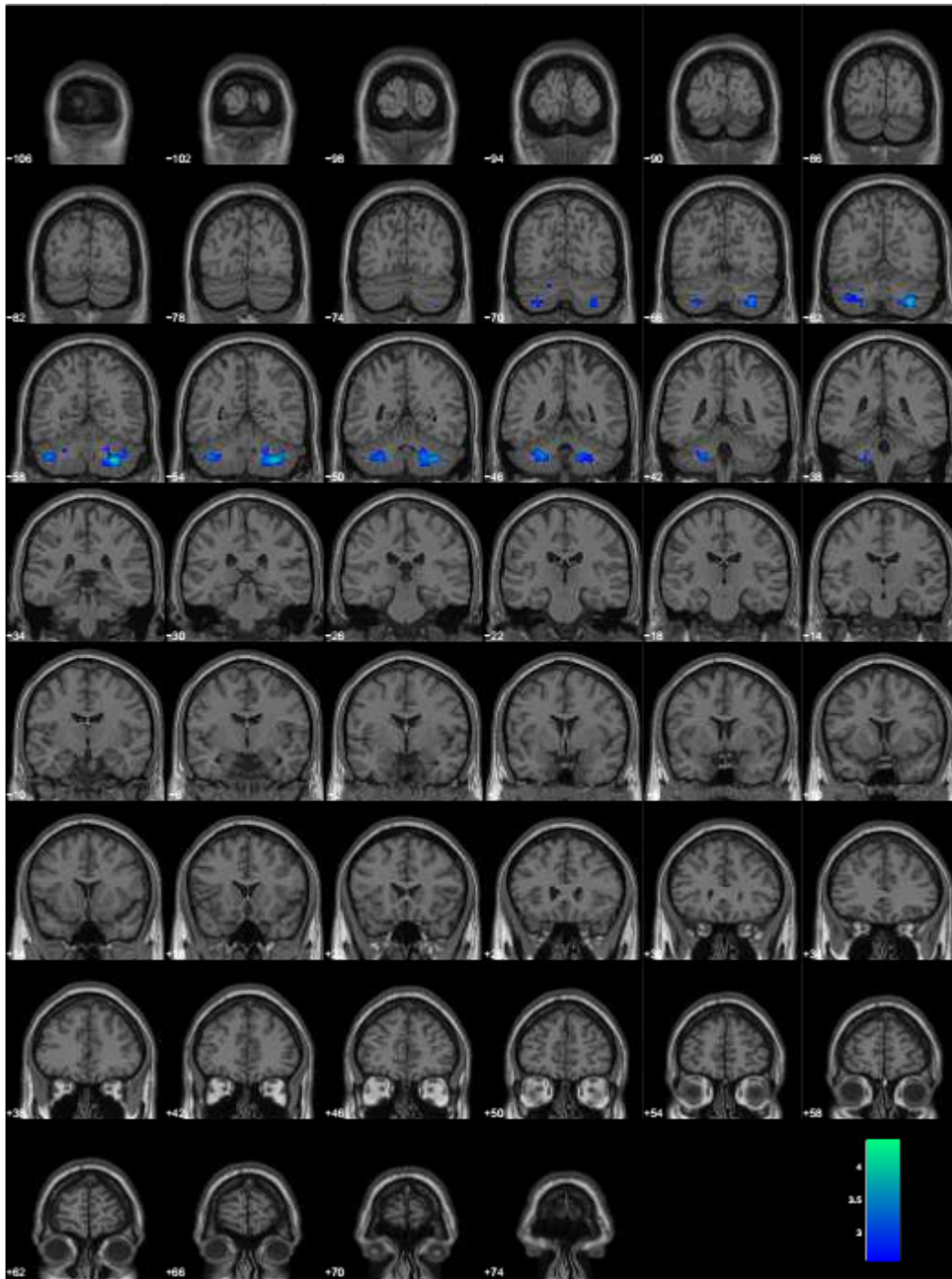
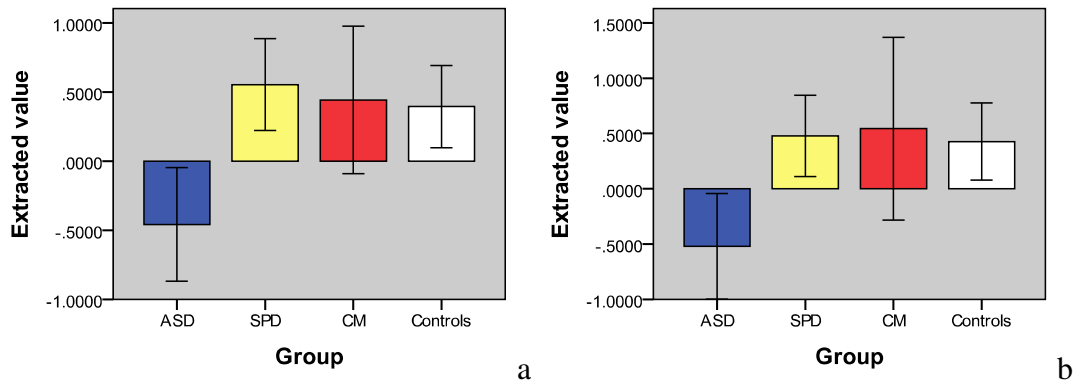**Figure 5.8:** Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and control groups.

Blue – green clusters represent areas of less activation increase in ASD compared to control group

Only clusters with a significance value of p<0.1 are displayed

Figure 5.9: Graphs showing difference values of extracted eigenvariates from (a) right cerebellum (30 -58 -44) and (b) left cerebellum (-45 -55 -41) clusters detailed in Table 5.6

Group x Condition Interaction: SPD versus Control

No significant clusters were seen for the SPD versus control group x condition interaction.

Group x Condition Interaction: CM versus Control

No significant clusters were seen for the CM versus control group x condition interaction.

Group x condition interaction: ASD versus SPD

Significantly greater activation was found in the SPD group compared to the ASD group when making social compared to gender judgements in several clusters covering the posterior cerebellum, fusiform and inferior temporal gyri bilaterally, and the left superior temporal gyrus, temporoparietal junction, precuneus and amygdala, and right hemisphere occipital regions (Table 5.7 and Figures 5.10 – 5.12).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
ASD > SPD						
No significant clusters						
ASD < SPD						
L. fusiform gyrus	-24	-52	-31	403	0.04	3.55
L. inferior temporal gyrus						
L. superior temporal gyrus						
L. precuneus						
L. cerebellum	-15	-40	-38	652	0.005	4.18
- anterior, VI, VIIa Crus I & II, VIIb						
R. cerebellum						
- anterior						
R. cerebellum	33	-64	-44	1554	<0.001	4.54
- VI, VIIa Crus I & VIIIb						
R. inferior occipital gyrus						
R. middle occipital gyrus						
R. fusiform gyrus						
R. inferior temporal gyrus						
L. amygdala	-18	-10	-14		0.046^{SVC}	3.00

Table 5.7: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and SPD groups.
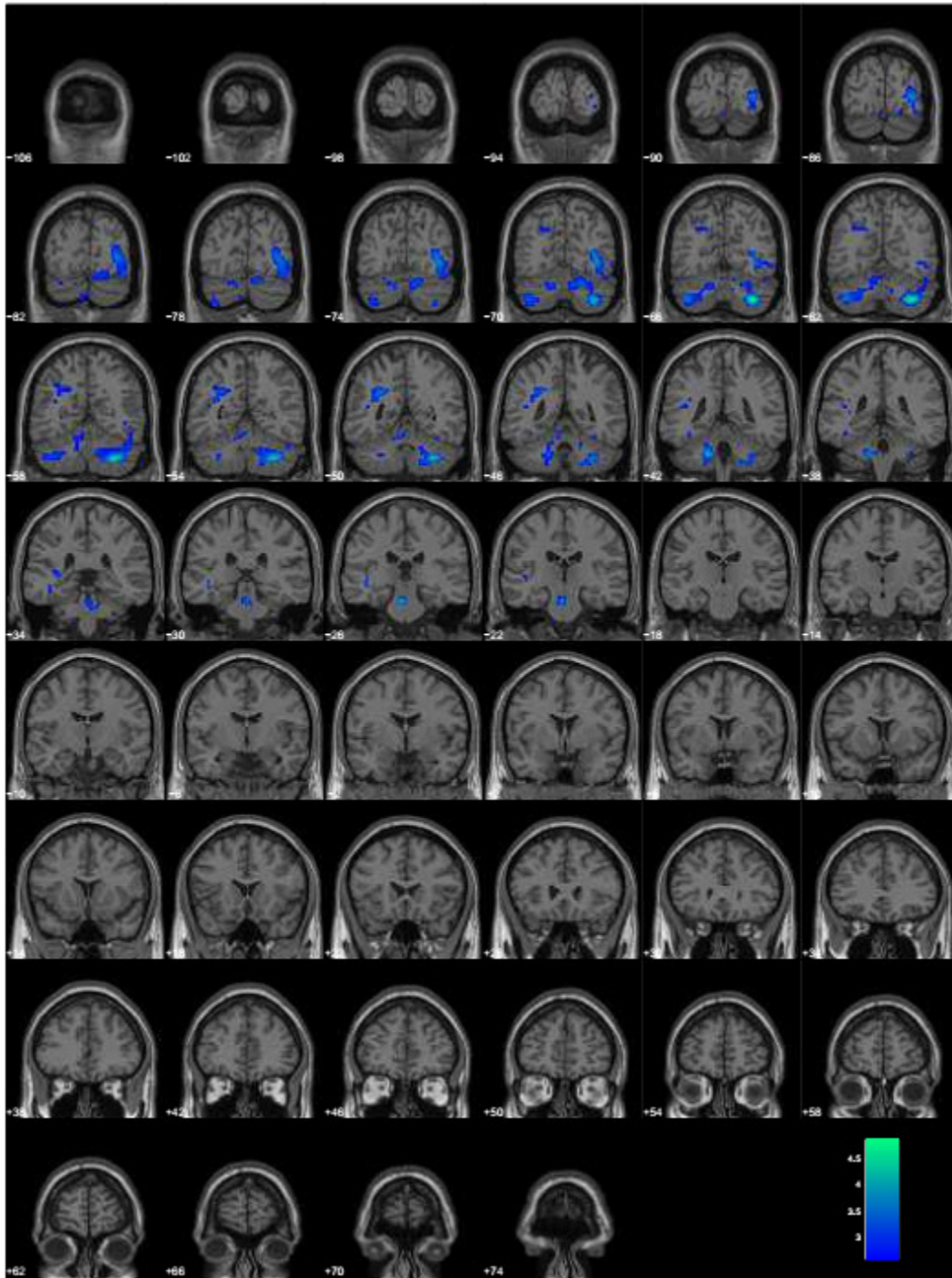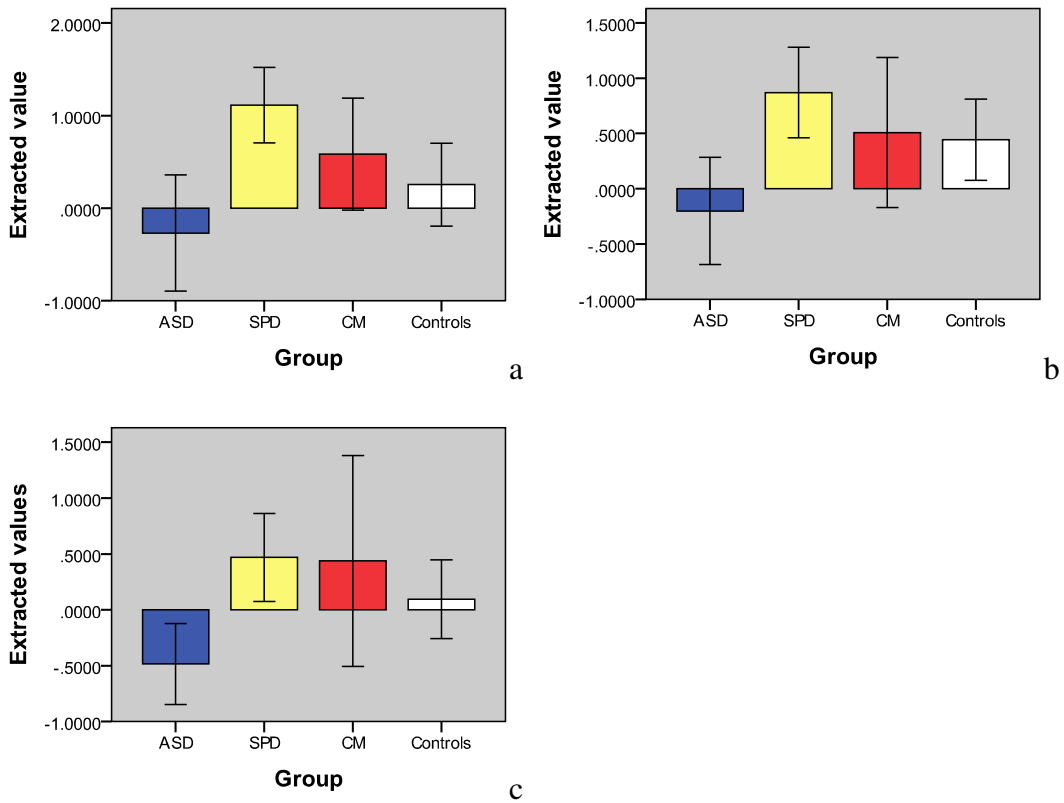
Figure 5.10: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and SPD groups.

Blue – green clusters represent areas of less activation increase in ASD compared to SPD group

Only clusters with a significance value of $p < 0.1$ are displayed

Figure 5.11: Graphs showing difference values of extracted eigenvariates from (a) temporoparietal cluster (-24 52 -31) (b) left cerebellum cluster (-15 -40 -38) and (c) right cerebellum cluster (33 -64 -44) detailed in Table 5.7
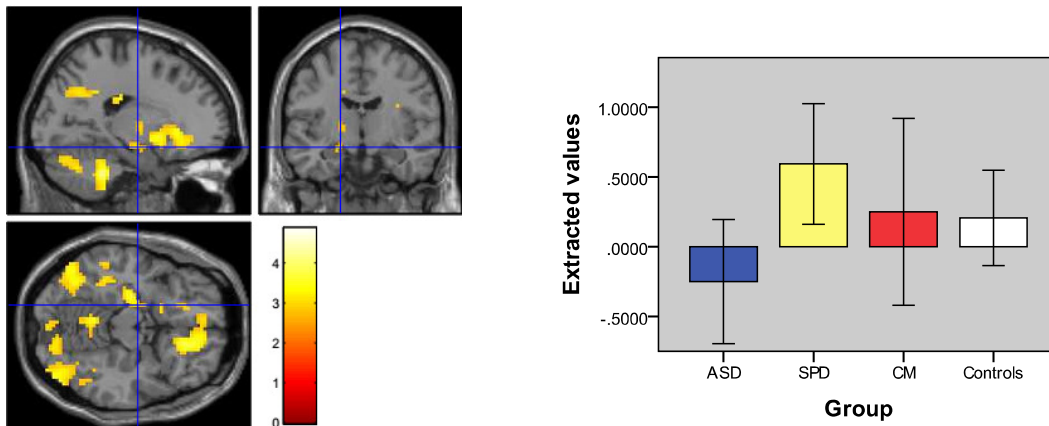
Figure 5.12: Location of increased amygdala activation (-18 10 14) and graph of difference values of extracted eigenvariates for social > gender contrast in SPD group versus ASD group

Group x condition interaction: ASD versus CM

The increase in activation in the social relative to the gender judgment was greater in the CM group compared to the ASD group in the left pre- and post-central gyri, the right cerebellum and cerebellar vermis (Table 5.8 and Figures 5.13 – 5.14)

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
ASD > CM						
No significant clusters						
ASD < CM						
L. postcentral gyrus	-18	-19	49	844	0.001	3.94
L. precentral gyrus						
L. superior frontal gyrus						
R. cerebellum (VI, VIIa, VIIb)	24	-55	-41	404	0.04	3.84
Cerebellar vermis (VIIIa)						

Table 5.8: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and CM groups.
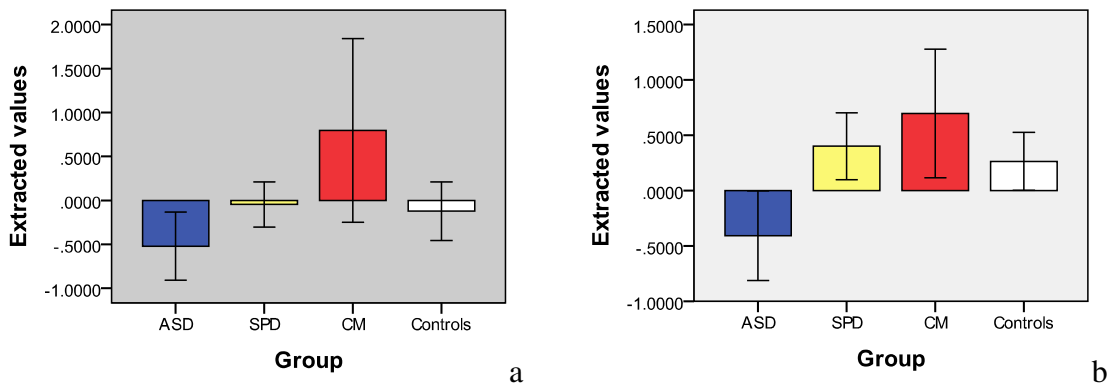

Figure 5.13: Graphs showing difference values of extracted eigenvariates from (a) frontal (-18 -19 49) and (b) cerebellum (24 -55 -41) clusters detailed in Table 5.8

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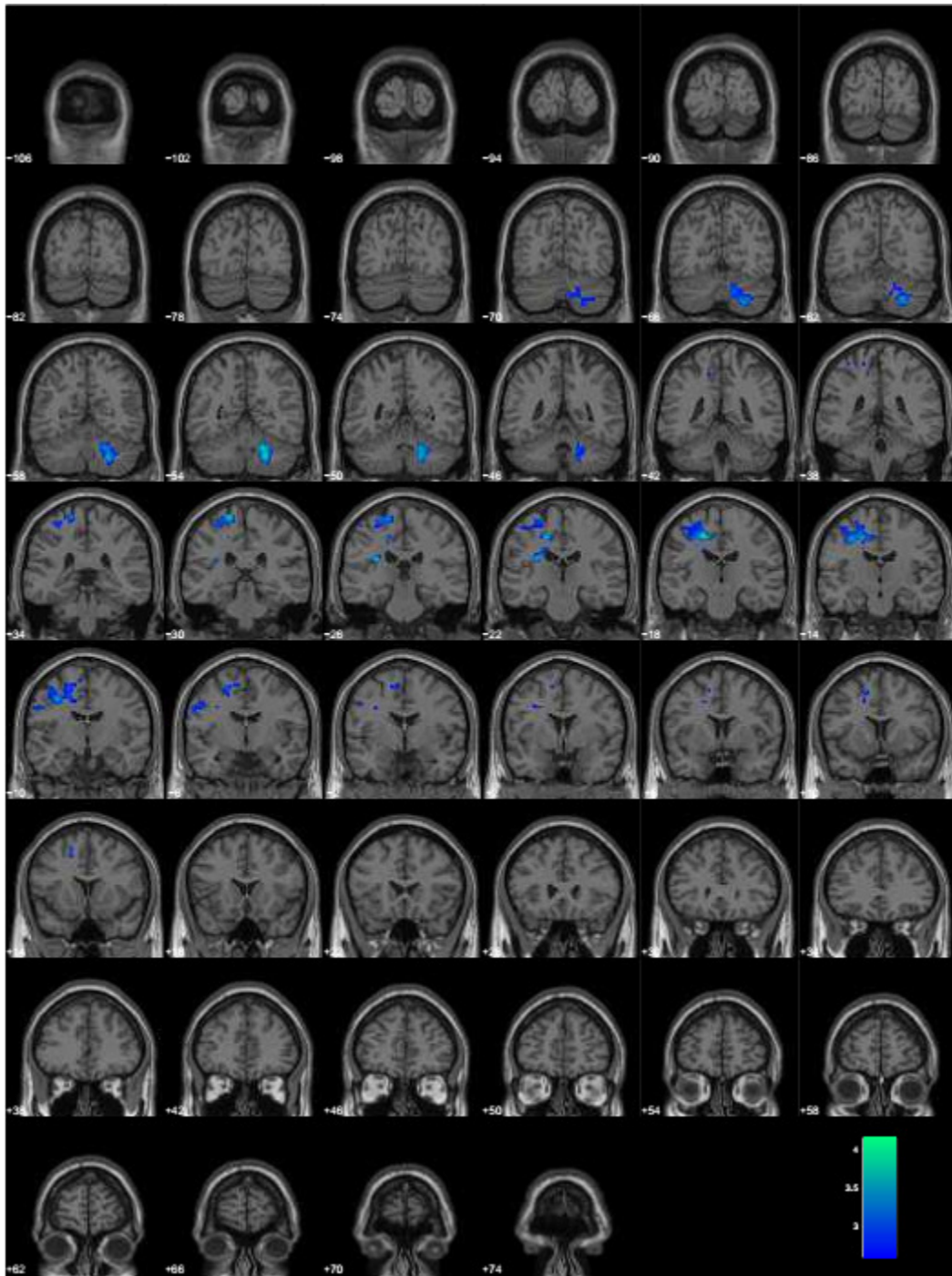
Figure 5.14: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and CM groups.

Blue–green clusters are areas of less activation change in ASD compared to CM group

Only clusters with a significance value of $p<0.1$ are displayed

Group x condition interaction: SPD versus CM

The SPD group displayed a trend towards significantly greater activation than the CM group in a cluster which extended from the dorsolateral prefrontal cortex around to the orbital frontal cortex, and included the right inferior frontal gyrus (Table 5.9 and Figures 5.15 – 5.16).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
SPD > CM						
R.inferior frontal gyrus - p. triangularis R. middle frontal gyrus R. superior frontal gyrus R. superior orbital gyrus	51	35	25	308	0.09	4.59
SPD < CM						
No significant clusters						

Table 5.9: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the ASD and CM groups.

Figure 5.15: Graph showing difference values of extracted eigenvariates from the frontal cluster (51 35 25) detailed in Table 5.8
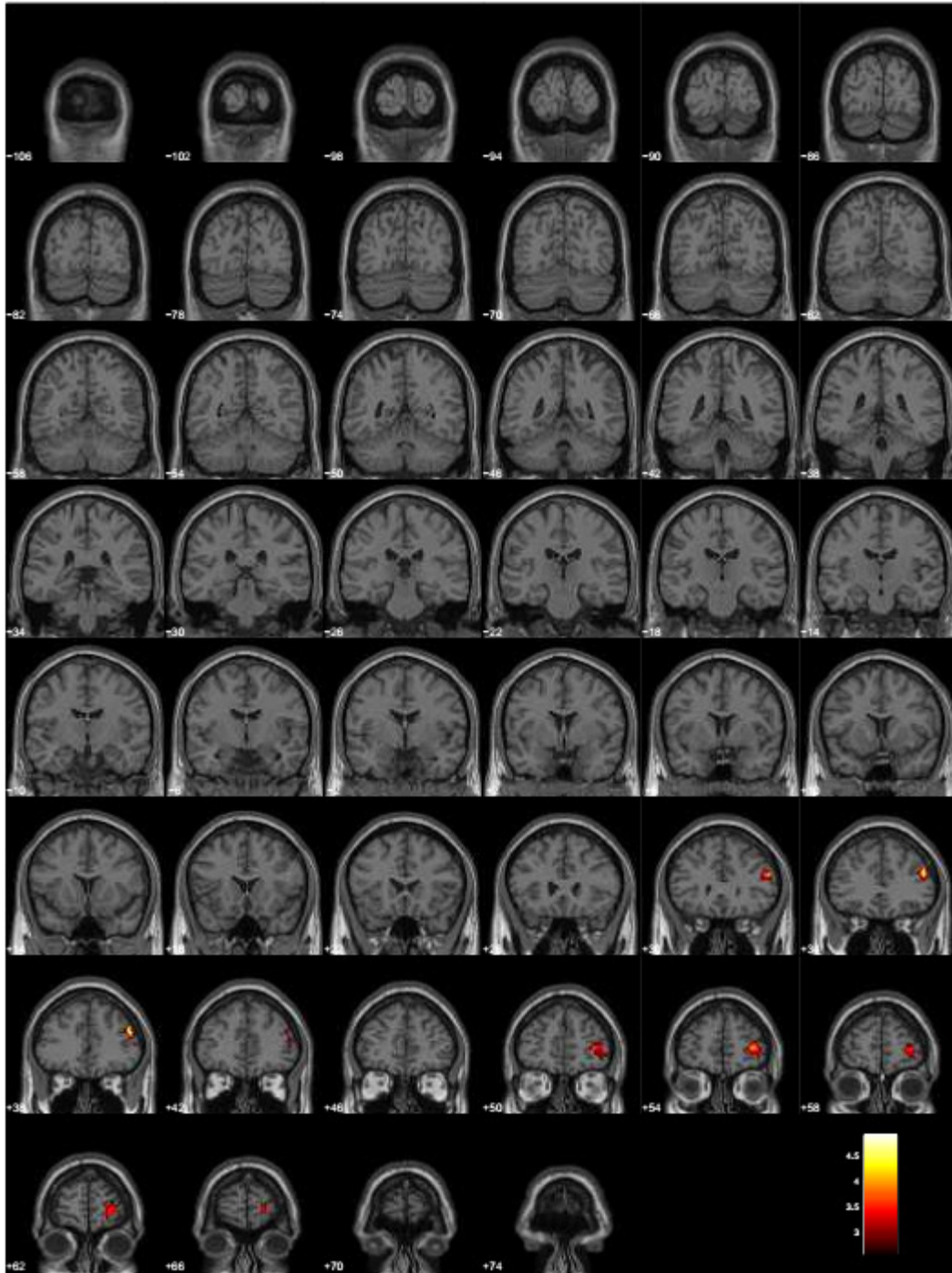
Figure 5.16: Brain regions showing differences in the relative increase in activation seen using the social > gender contrast between the SPD and CM groups.

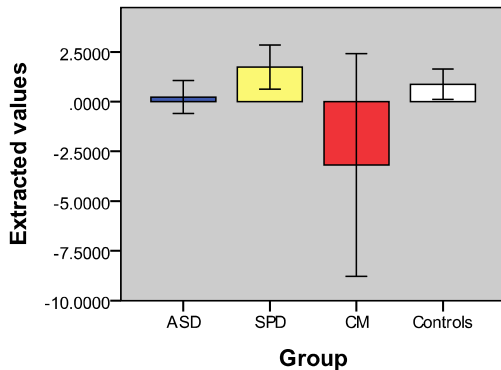Red-yellow clusters represent areas of greater activation change in SPD compared to CM group

Only clusters with a significance value of $p < 0.1$ are displayed

5.3.2.5: Analysis of potential confounding factors

In order to assess the effect of potential confounding variables, the difference between the extracted eigenvariates of the social and gender conditions was regressed against IQ and performance on the approachability task, with group as a covariate. No significant relationships were seen, suggesting that the reported differences are not due to performance or IQ differences between the groups.

5.3.2.6: Relationship between clinical traits and extracted difference values

There was a trend towards a significant difference between the groups in the relationship between the extracted value for the left frontal cluster identified in the ASD < CM contrast (MNI -18 -19 49) and negative symptoms as measured by the SIS (p=0.08). A significant positive relationship was seen between these measures in the CM group (r=0.69, p=0.03) while a trend towards a significant negative relationship was seen in the SPD group (r=-0.40, p=0.09). No significant relationships were seen in the ASD or control groups (both p >0.26) (Figure 5.17a)

A trend towards a significant interaction for the same cluster was also seen for disorganised schizotypal traits (p=0.08). In this case however, the ASD group showed a trend towards a significant negative relationship (r=-0.35, p=0.09) whereas the other groups showed no significant relationships (all p> 0.17) (Figure 5.17b).

No other significant group x activation interaction effects on clinical traits were identified.
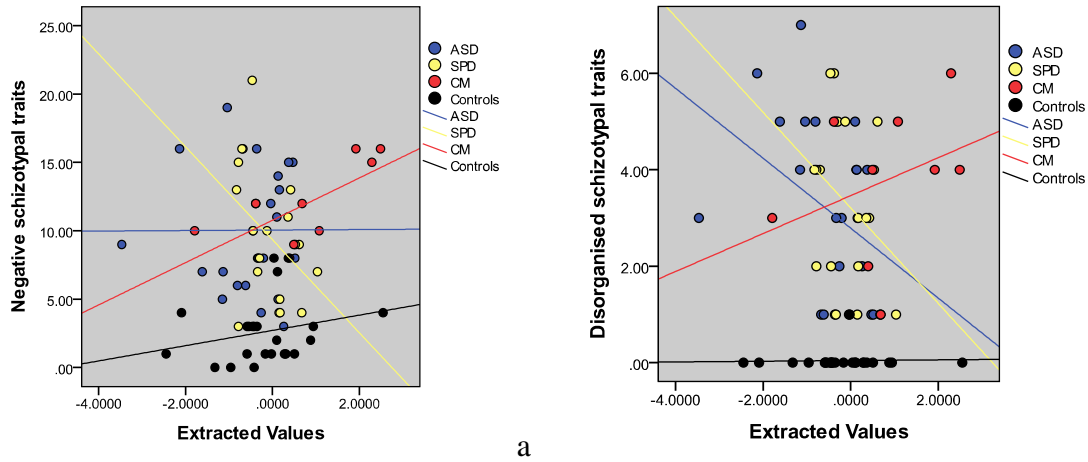
Figure 5.17: Graphs demonstrating relationship of (a) negative and (b) disorganised schizotypal traits with difference values of eigenvariates extracted from cluster located at MNI co-ordinate -18 -19 49, identified in ASD < CM contrast.

5.3.3: N-back task analysis

5.3.3.1: Performance

The scores for each group did not differ significantly in the 0-back and 1-back conditions. For the 2-back there was a trend towards a significant main effect of group (F=2.57, p=0.06) with the controls achieving higher scores than the ASD, SPD and CM groups (p=0.06, 0.06 and 0.02 respectively). For the 3-back condition, there was again a trend towards a significant main effect (F=2.19, p=0.097), with the SPD group performing significantly less well than the controls (p=0.02) and the CM showing a trend towards significantly reduced performance compared to the controls (p=0.097). There were no other significant differences between the groups.
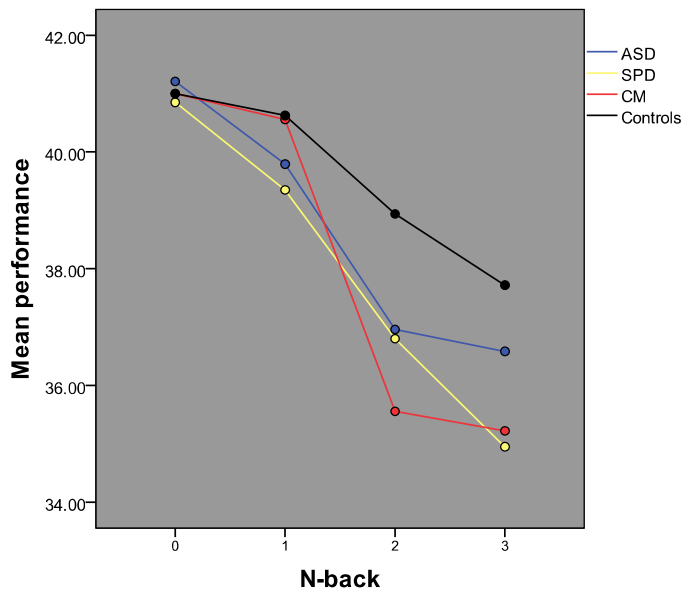
Figure 5.18: Performance on the n-back working memory task as working memory load

increased from 0-back to the 3-back condition

5.3.3.2: Main effect of condition

The main effect of condition is a measure of the change in brain activation as working memory (WM) load increases across the conditions (i.e. 1-back up to 3-back) in all four groups considered together. Increasing WM load was associated with increased activations located mainly in the dorsolateral and superior medial frontal cortex, parietal lobes, basal ganglia and the posterior cerebellum (Table 5.10 and Figure 5.19). Reductions in activation were seen in the anterior, middle and posterior cingulate, insula, superior temporal gyrus, pre- and post-central gyri, fusiform gyri and parahippocampus (Tables 5.11 and Figure 5.19).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Increasing activation						
L. & R. middle frontal gyrus	-30	8	58	5994	<0.001	∞
L. supplementary motor area						
L. & R. precentral gyrus						
L. & R. inferior frontal gyrus						
- p. opercularis and p. orbitalis						
R. orbital gyrus						
R. inferior medial frontal gyrus						
L. insula						
L. & R. caudate						
L. & R. inferior parietal lobule	-33	-58	43	2772	<0.001	∞
R. supramarginal gyrus						
R. angular gyrus						
L. & R. precuneus						
R. cerebellum	36	-64	-32	116	0.07	5.75
- VI & VIIa						

Table 5.10: Brain regions showing increasing activation as WM load increased when all subjects considered together

Regions	MNI of peak			Extent	P$_{FWE}$	Z$_{peak}$
Decreasing activation						
R. supramarginal gyrus	57	-28	19	1358	<0.001	7.51
R. superior temporal gyrus						
R. insula						
R. postcentral gyrus						
R. precentral gyrus						
R. temporal pole						
L. posterior cingulate	-6	-52	22	3522	<0.001	6.97
R. precentral gyrus						
L. & R. postcentral gyrus						
L. & R. middle cingulate						
L. superior parietal lobule						
L. & R. paracentral lobule						
L. & R. fusiform gyrus						
R. anterior cerebellum						
R. parahippocampus						
L. inferior medial frontal gyrus	-6	59	7	595	<0.001	6.57
L anterior cingulate						
L. superior frontal gyrus						
L. superior temporal gyrus	-54	-28	10	789	<0.001	5.91
L. insula						
L. angular gyrus	-54	-70	25	126	0.06	4.96
L middle temporal gyrus						

Table 5.11: Brain regions showing decreasing activation as WM load increased
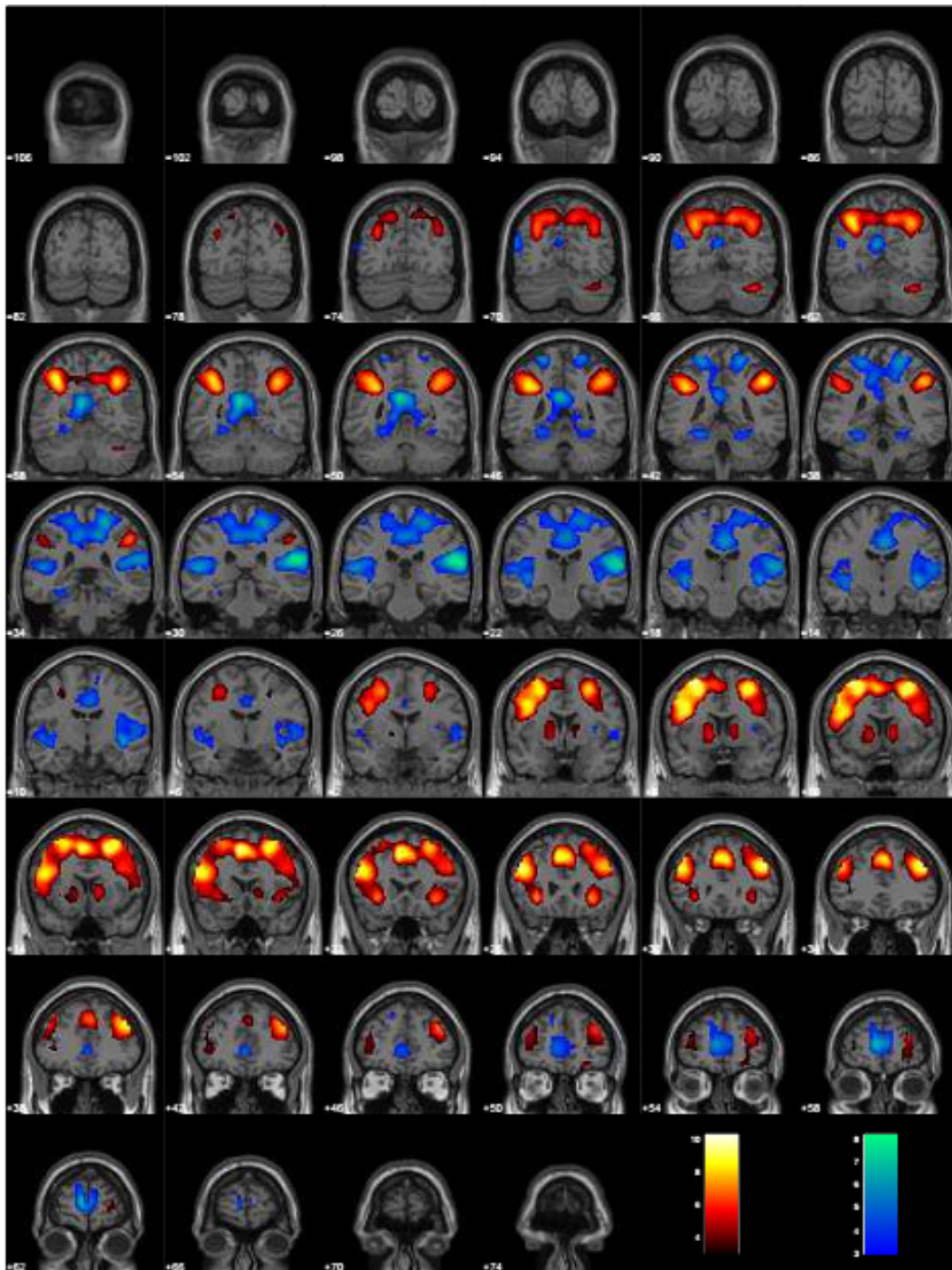
Figure 5.19: Regions showing changes in activation as WM load increases

Red-yellow – increasing activation; blue-green – decreasing activation

Only clusters with a significance value of p<0.1 are displayed

5.3.3.3: Brain activation within each group

Within Controls

Similar to the main effect of condition analysis, controls showed increases in activation in dorsolateral and superior medial frontal regions, parietal regions, basal ganglia and the cerebellum as WM load increased (Table 5.12 and Figure 5.20).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Increasing activation						
L. inferior frontal gyrus	-45	17	19	5178	<0.001	∞
- p. opercularis & p. triangularis						
R. middle frontal gyrus						
L. & R. superior frontal gyrus						
L. & R. precentral gyrus						
L. supplementary motor area						
L. & R. insula						
L. globus pallidus						
R. caudate						
L. inferior parietal lobule	-33	-58	43	3431	<0.001	7.75
R. supramarginal gyrus						
R. precuneus						
L. superior parietal lobule						
R. angular gyrus						
R. cerebellum	33	-64	-35	472	<0.001	6.26
- VI, VIIa Crus I &II						
L. lingual gyrus	-15	-97	-11	151	0.04	4.58
R. lingual gyrus	21	-91	-8	107	0.09	4.31
R. calcarine gyrus						
Cerebellar vermis	-3	-25	20	114	0.08	4.07

Table 5.12: Brain regions showing increasing activation within controls as WM load increased

Decreases in activation were also found in similar regions to the main effect of condition analysis: midline regions, the superior temporal lobe and insula (Table 5.13 and Figure 5.20).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Decreasing activation						
R. supramarginal gyrus	57	-28	19	800	<0.001	6.02
R. rolandic operculum						
R. insula						
R. superior temporal gyrus						
L. superior medial frontal gyrus	-6	59	7	593	<0.001	5.89
L. anterior cingulate						
L. superior frontal gyrus						
L. superior temporal gyrus	-39	-16	-5	484	<0.001	5.66
L. temporal pole						
L. amygdala						
L. posterior cingulate	-3	-52	25	200	0.02	5.49
L. & R. postcentral gyrus	18	-37	64	1060	<0.001	5.40
R. paracentral lobule						
R. supplementary motor area						

Table 5.13: Brain regions showing decreasing activation within controls as WM load increased
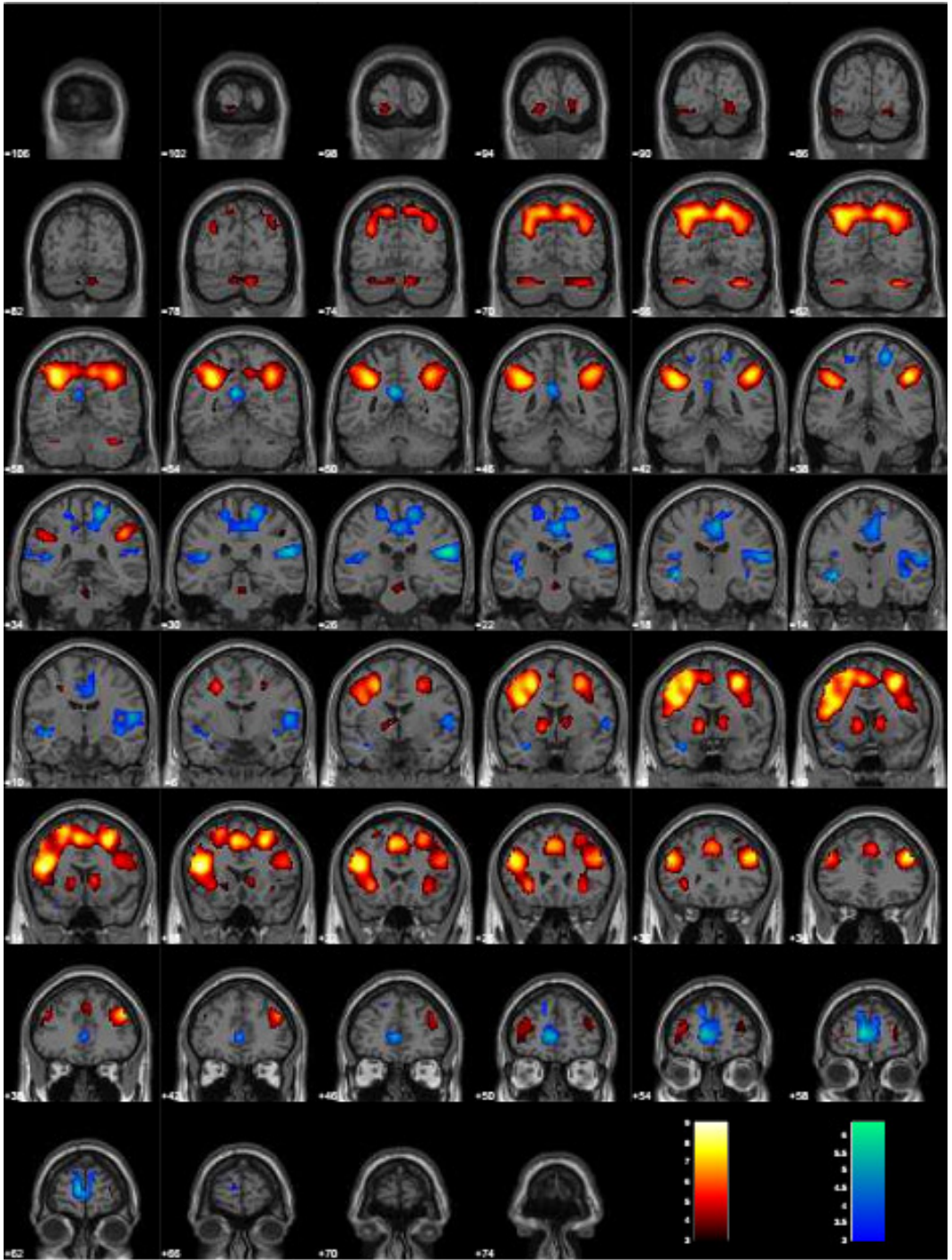
Figure 5.20: Regions showing changes in activation within control group as WM load increases

Red-yellow – increasing activation; blue-green – decreasing activation

Only clusters with a significance value of p<0.1 are displayed

Within ASD group

AS WM load increased, the ASD group showed increases in activation in dorsolateral and superior medial frontal regions, as well as in the parietal lobe (Table 5.14 and Figure 5.21)

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Increasing activation						
L. inferior frontal gyrus - p.triangularis & p. opercularis L. middle frontal gyrus L. supplementary motor area L. superior medial frontal gyrus	-48	26	28	1023	<0.001	5.86
R. middle frontal gyrus	30	8	55	232	<0.001	5.11
R. inferior frontal gyrus - p. triangularis R. middle frontal gyrus	45	32	28	177	0.02	4.87
L. inferior parietal lobule L. angular gyrus	-36	-58	46	167	0.03	4.12
R. supramarginal gyrus R. angular gyrus R. inferior parietal lobule	48	-40	40	194	0.02	4.11

Table 5.14: Brain regions showing increasing activation within ASD group as WM load increased

Decreases in activation within the ASD group as WM load increased were seen in the cingulate gyrus, anterior superior medial frontal lobe, superior temporal regions, insula, postcentral gyrus and occipital regions (Table 5.15 and Figure 5.21).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Decreasing activation						
L. posterior cingulate	-6	-52	22	2022	<0.001	5.70
R. paracentral lobule						
L. superior parietal lobule						
L. & R. postcentral gyrus						
L. middle cingulate						
L. calcarine gyrus						
R. rolandic operculum	57	-28	22	476	<0.001	4.90
R. insula						
L. middle temporal gyrus	-51	-70	19	123	0.06	4.43
L. occipital gyrus						
L. superior temporal gyrus	-39	-25	-2	272	0.004	4.22
L. insula						
L. & R. superior medial frontal gyrus	9	56	13	103	0.095	3.91
L. anterior cingulate						

Table 5.15: Brain regions showing decreasing activation within ASD group as WM load increased
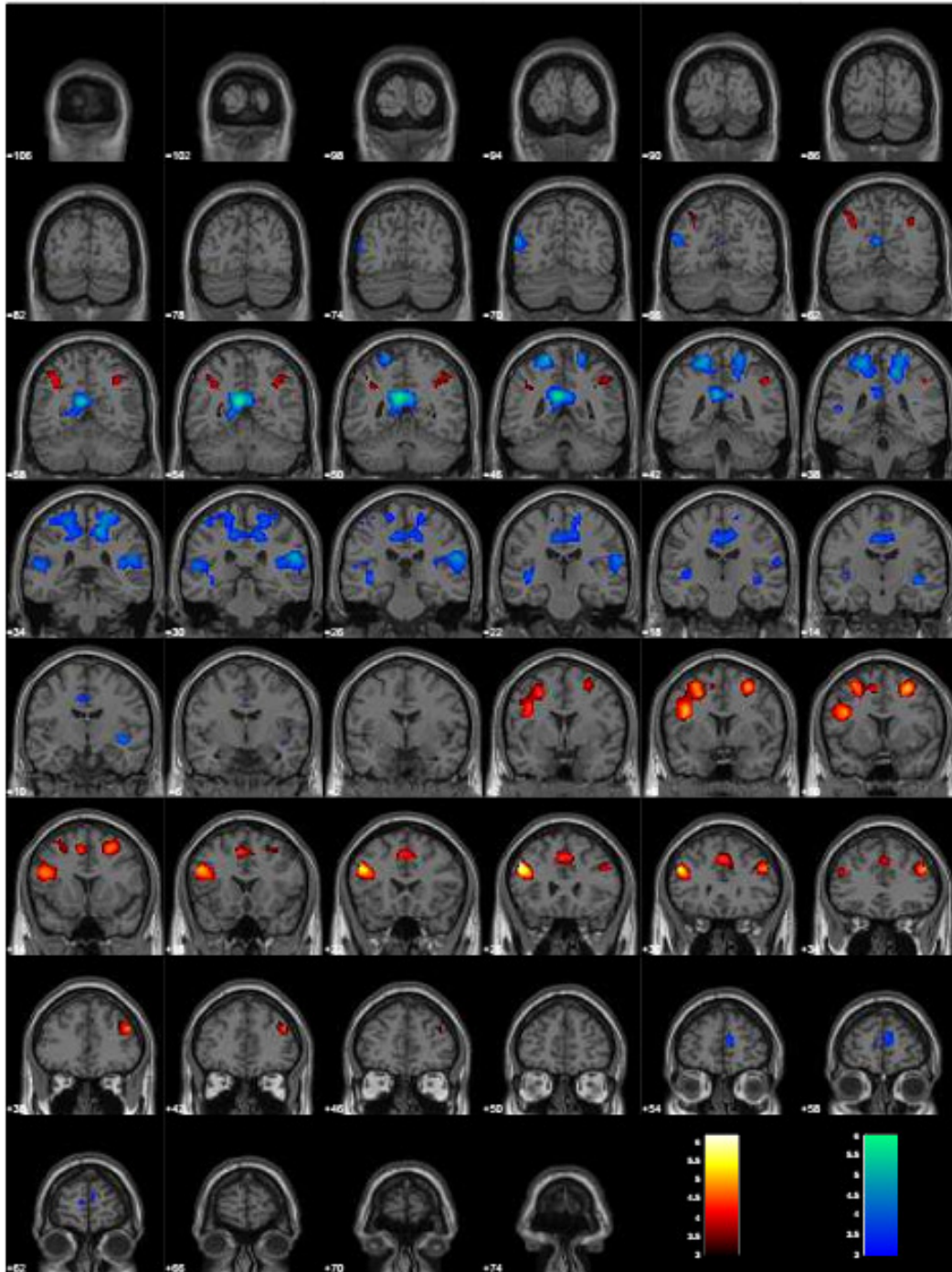
Figure 5.21: Regions in ASD group showing changes in activation as WM load increases

Red-yellow – increasing activation; blue-green – decreasing activation

Only clusters with a significance value of p<0.1 are displayed

Within the SPD group, increasing WM load was associated with increasing activity in the dorsolateral and superior medial frontal cortex and the parietal lobe (Table 5.16 and Figure 5.22).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Increasing activation						
L. supplementary motor area	-3	17	49	1714	<0.001	7.12
L. middle frontal gyrus						
L. inferior frontal gyrus						
- p. triangularis						
L. precentral gyrus						
R. middle frontal gyrus	45	35	31	953	<0.001	6.16
R. inferior frontal gyrus						
- p. opercularis						
L. inferior parietal lobule	-33	-46	37	742	<0.001	5.65
L. superior parietal lobule						
R. angular gyrus	36	-64	40	747	<0.001	5.64
R. supramarginal gyrus						
R. precuneus						

Table 5.16: Brain regions showing increasing activation within SPD group as WM load increased

Reductions in activity as WM load increased were seen in the anterior superior medial frontal lobe, cingulate gyrus, insula and superior temporal regions (Table 5.17 and Figure 5.22).

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Decreasing activation						
R. rolandic operculum	54	-28	22	1263	<0.001	6.94
R. supramarginal gyrus						
R. superior temporal gyrus						
R. Heschl's gyrus						
R. insula						
L. anterior cingulate	0	41	1	479	<0.001	6.06
L & R. superior medial frontal gyrus						
L. superior frontal gyrus						
L. posterior cingulate	-6	-52	22	2242	<0.001	5.73
L. & R. fusiform gyrus						
L. calcarine gyrus						
R. postcentral gyrus						
L. & R. middle cingulate cortex						
R. middle temporal gyrus						
R. paracentral lobule						
L. superior temporal gyrus	-54	-31	10	665	<0.001	5.14
L. insula						

Table 5.17: Brain regions showing decreasing activation within SPD group as WM load increased
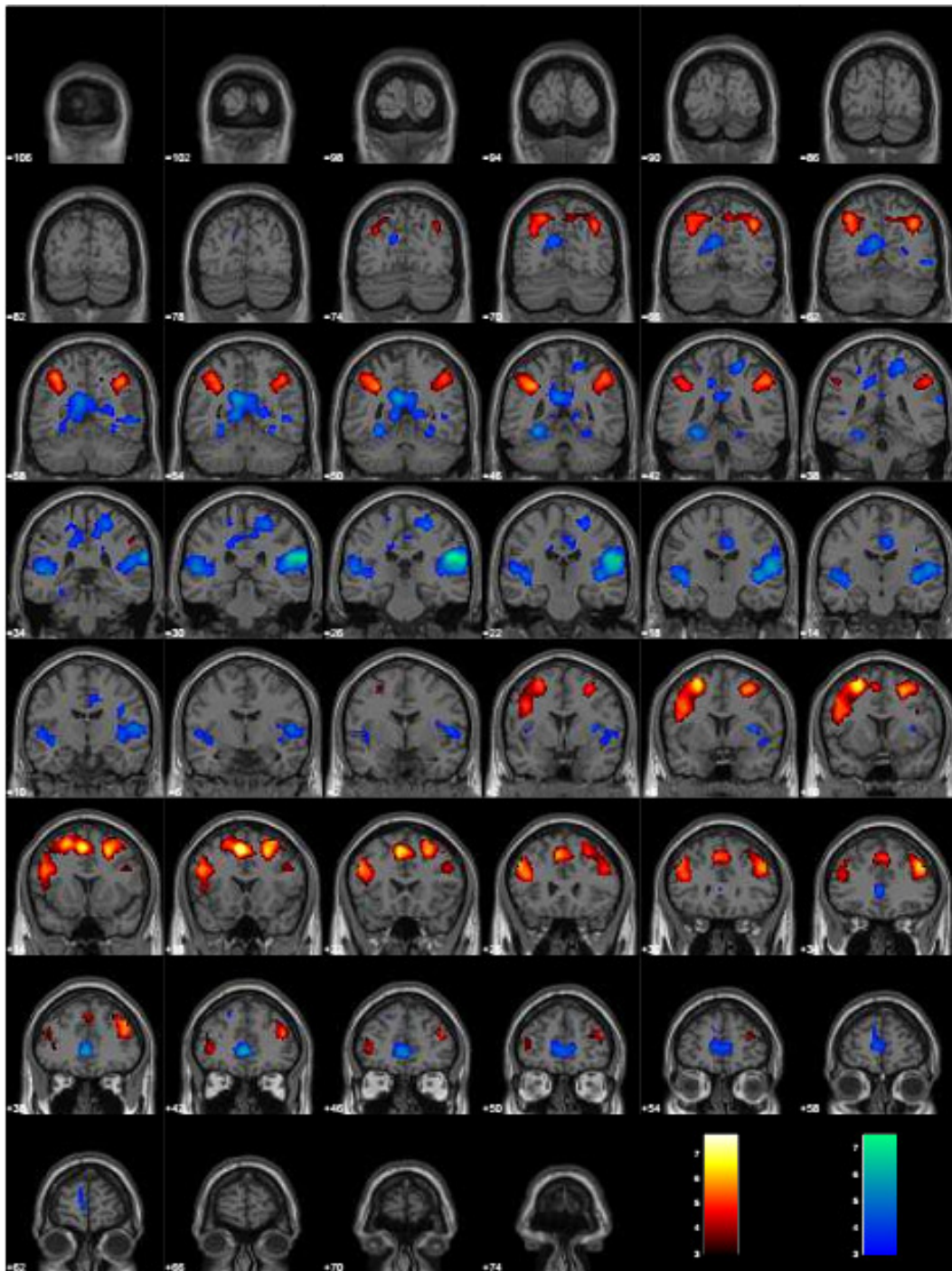
Figure 5.22: Regions in SPD group showing changes in activation as WM load increases

Red-yellow – increasing activation; blue-green – decreasing activation

Only clusters with a significance value of p<0.1 are displayed

Within CM group

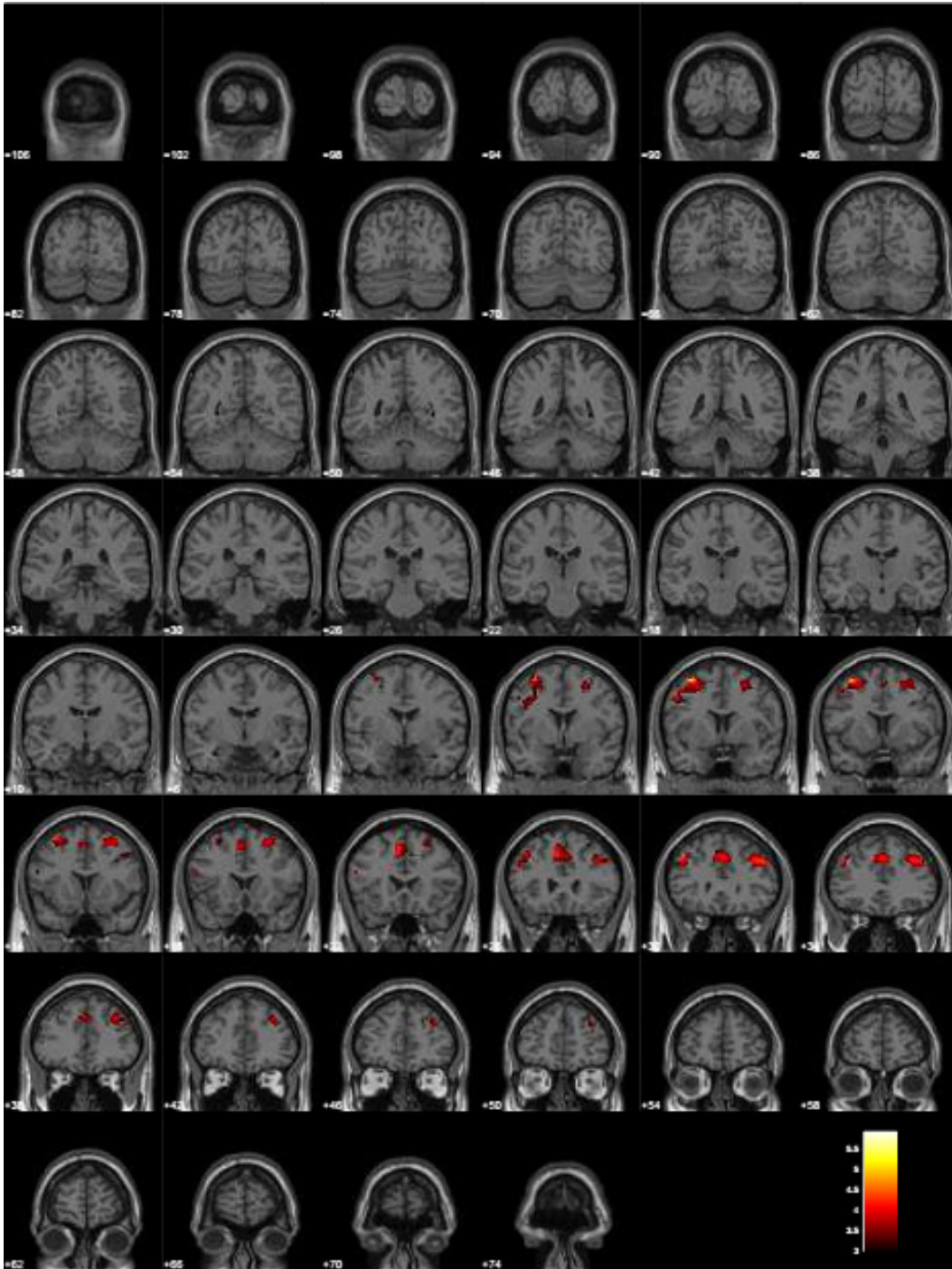As WM load increased the CM group showed increases in activation in the dorsolateral and superior medial frontal regions (table 5.17 and Figure 5.23). There were no regions in which significant decreases in brain activation during increasing WM load were seen.

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
Increasing activation						
L. middle frontal gyrus	-36	8	61	323	0.002	5.65
L. precentral gyrus						
L inferior frontal gyrus						
- p. opercularis						
L. middle frontal gyrus	-42	32	40	111	0.08	4.62
L. inferior frontal gyrus						
- p. triangularis						
R. middle frontal gyrus	48	32	34	254	0.006	4.43
R. inferior frontal gyrus						
- p. opercularis						
L. superior medial gyrus	-6	23	43	276	0.004	4.30
R. supplementary motor area						
R. middle frontal gyrus	24	17	52	180	0.02	3.93
R. superior frontal gyrus						

Table 5.17: Brain regions showing increasing activation within CM group as WM load increased

Figure 5.23: Regions in CM group showing changes in activation as WM load increases

Red-yellow – increasing activation; no regions of decreasing activation were seen

Only clusters with a significance value of p<0.1 are displayed

5.3.3.4: Group x condition interaction: increasing WM load

ASD versus Control

Significantly less increase in activation was seen in the ASD group compared to controls as WM load increased in a cluster which stretched from the left superior parietal lobule into the cuneus and calcarine gyrus (Table 5.18 and Figures 5.24-5.25). Note that this cluster may also result from greater decrease in activation in the ASD group as WM load increases. No significantly greater increases in activation were seen in the ASD group.

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
ASD > Control						
No significant clusters						
ASD < Control						
L. superior parietal lobule	-21	-49	40	612	0.004	3.63
L. calcarine gyrus						
L. cuneus						

Table 5.18: Brain regions showing differences in the degree of increased activation between the ASD and control groups as WM load increases
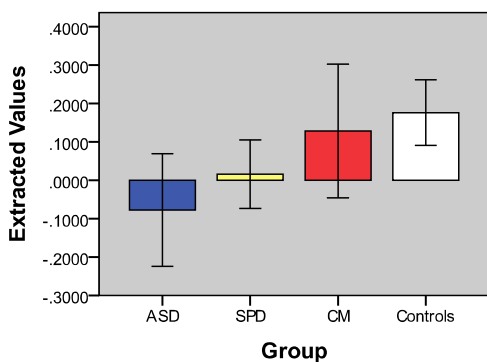
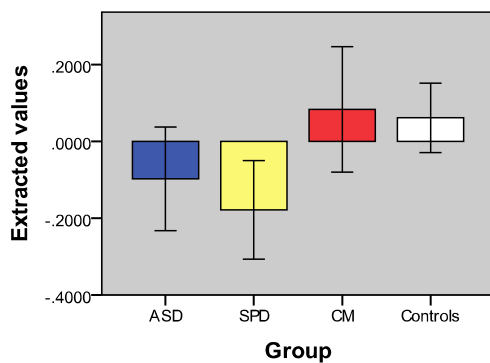**Figure 5.24:** Extracted values of cluster at (-21 -49 40) detailed in Table 5.18
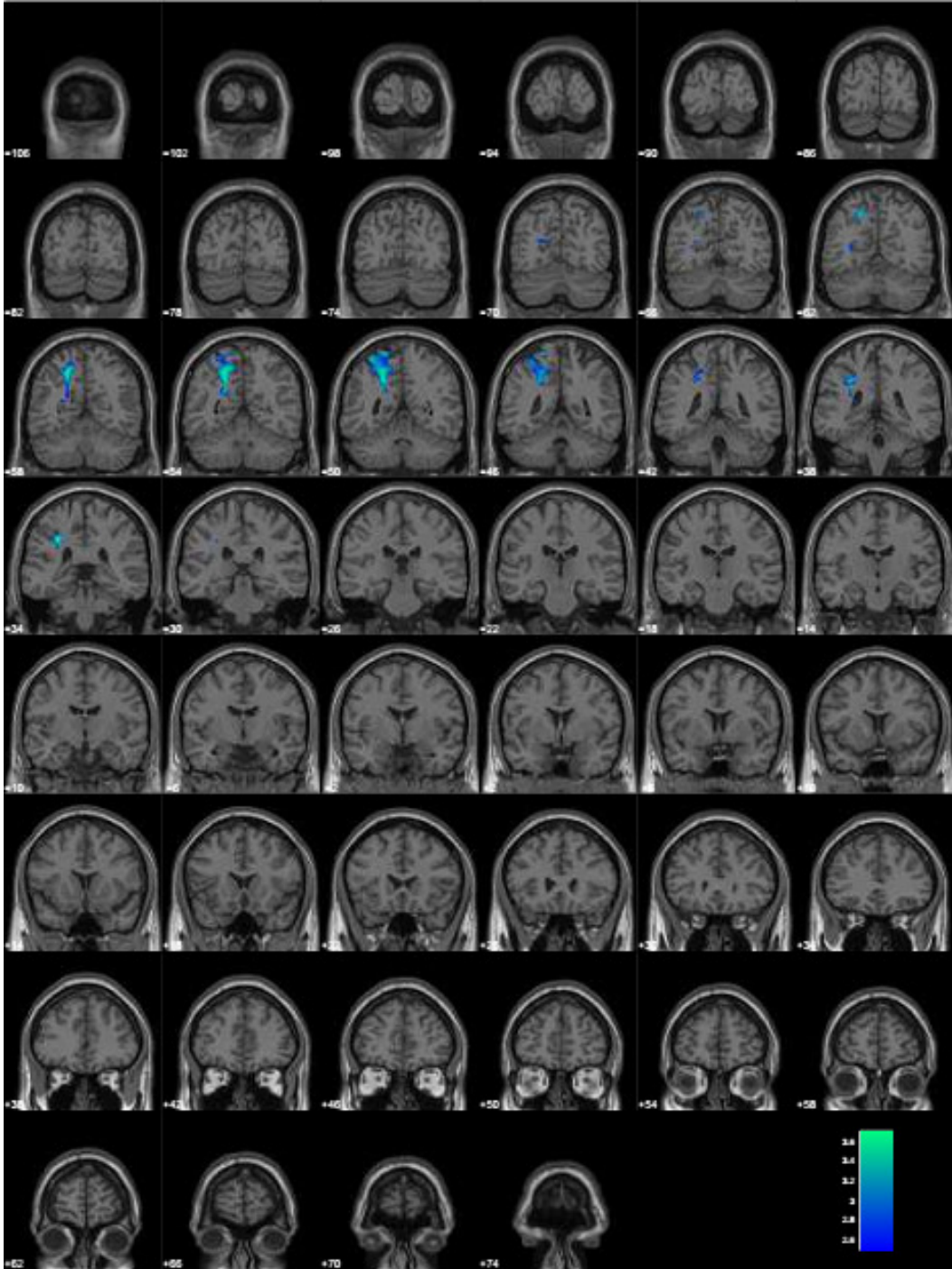
Figure 5.25: Cluster of significantly less increase in activation in the ASD group compared to the controls

SPD versus Control

Significantly less increase in activation was seen in a bilateral parietal-occipital cluster in the SPD group compared to the control group as WM load increased (Table 5.19 and Figures 5.26 – 5.27). This pattern of differences could also be caused by a significantly greater decrease in activation in the SPD group as WM load increases. No other significant differences were seen.

Regions	MNI of peak			Extent	P_{FWE}	Z_{peak}
SPD > Control						
No significant clusters						
SPD < Control						
L. & R. calcarine gyrus	-21	-67	16	946	<0.001	4.25
L. cuneus						
L. & R. precuneus						
R. middle temporal gyrus						
R. lingual gyrus						

Table 5.19: Brain regions showing differences in the degree of increased activation between the SPD and control groups as WM load increases

Figure 5.26: Extracted values of cluster at (-21 -67 16) detailed in Table 5.19

Figure 5.27: Cluster of significantly less increase in activation in the SPD group compared to the controls

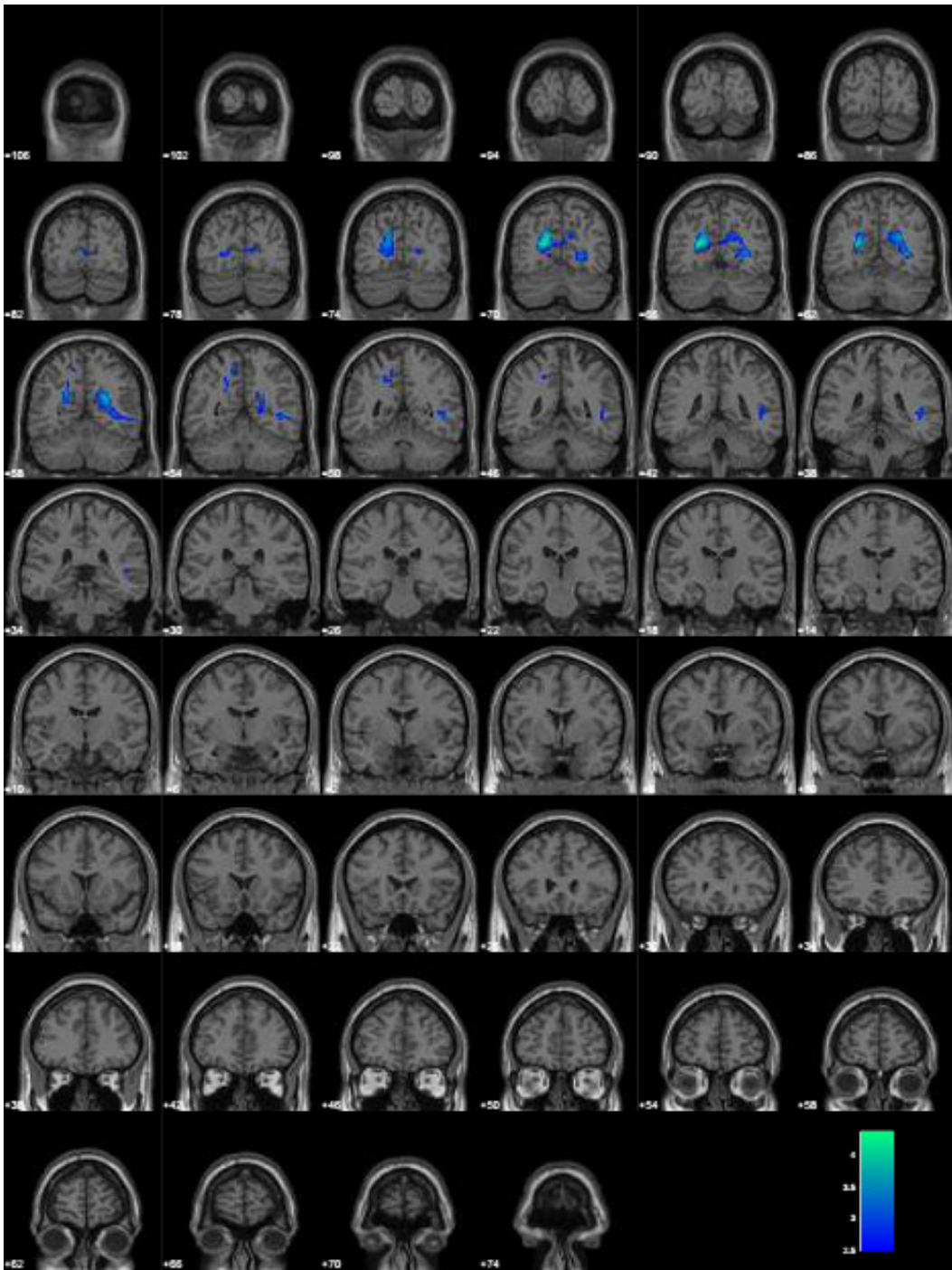*Other group x condition interactions*

No significant differences were seen in any of the other group x condition interactions (CM versus control, ASD versus SPD, ASD versus CM and SPD versus CM).

5.3.3.5: Examination of potential confounding factors

Partial correlations controlling for group revealed no significant relationships between activation in the two clusters identified as differing between the groups and either IQ or task performance at any level (all p>0.22).

5.3.3.6: Relationship between clinical traits and extracted difference values

There was a significant interaction between positive schizotypal traits, as measured by the SIS, and activation in the parieto-occipital cluster identified in the SPD < Control analysis (p=0.04). The SPD group showed a significant negative relationship between activation difference in this cluster and increasing positive symptoms (r=-0.48, p=0.04): i.e. worse positive symptoms were associated with less of an increase in activation (or a greater decrease in activation) in this region. No significant relationships were seen in the other groups (r=-0.30, p=-.16 for ASD; r=-0.27, p=0.49 for CM; and r=0.11, p=0.64 for controls) although inspection of the scatterplot suggested that the greatest difference was between the SPD group and the CM group (Figure 5.28). No other significant interactions were seen for any of the clusters.
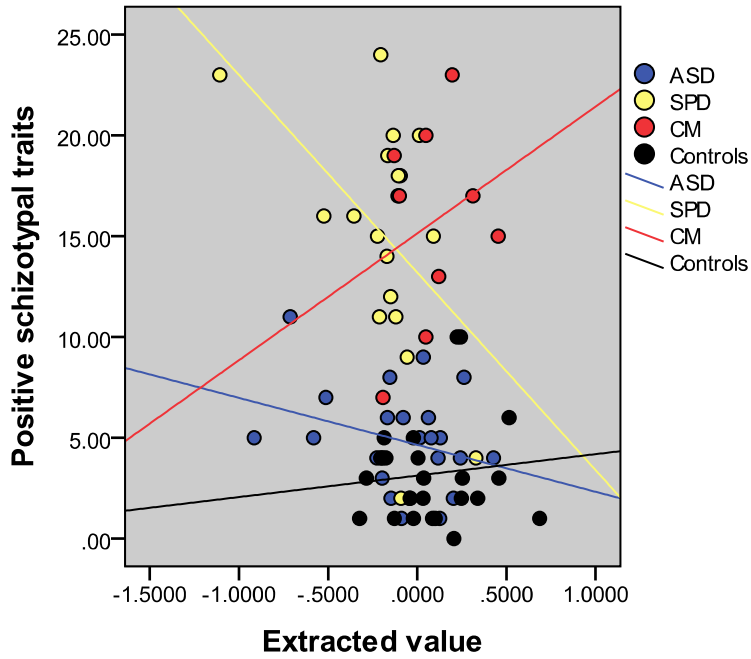
Figure 5.28: Relationship of positive schizotypal traits with difference values of eigenvariates extracted from temporo-parieto-occipital cluster (peak: MNI -21 -67 16), identified in the n-back task SPD < Control contrast.

5.4: DISCUSSION

Consistent with the hypothesis, differences were found between people with ASD and those with SPD in relation to the social judgment task. Despite similar behavioural performance in the ASD and SPD groups, fMRI revealed clear differences between them when making judgements of approachability compared to judgments of gender in regions of the brain known to be associated with social cognition: the fusiform gyrus, precuneus, temporoparietal junction and amygdala. This marked difference in social brain function stands in contrast to the results identified using the n-back task where there were no significant differences between the ASD, SPD and CM groups.

Social judgment task

For the social judgement tasks, when all participants were considered together, greater activations in the social condition compared to the gender condition were seen in many of the social brain regions reviewed in Chapter 2 suggesting that the task reliably taps social cognitive functions. The regions activated included the inferior frontal gyrus, medial prefrontal lobe, temporoparietal junction, temporal pole, insula, amygdala and posterior cerebellum. When the within group activation maps were considered, the SPD group and to a lesser extent the controls showed activations within many of these regions. In contrast the ASD group and the CM group showed little, if any increases in activation when making social compared to gender judgments.

This impression of greater activity in the SPD compared to the ASD group was borne out by the between group comparisons where significantly increased activation was seen in

people with SPD compared to those with ASD in the precuneus, temporoparietal junction, fusiform gyrus, visual cortex (mainly ventral V3 and V4), amygdala and posterior cerebellum in the social > gender contrast. These differences in social brain regions suggest that the mentalising deficits which occur in both groups are associated with different underlying mechanisms and imply that, from a social perspective at least, ASD and SPD are potentially quite different conditions.

Although there were few significant clinical group – control differences apparent, inspection of the graphs of the extracted eigenvariate difference values shows that for many of these regions the SPD group show the greatest activity, the ASD group the least and the controls sitting between them. This is broadly consistent with the hypo- and hyper-mentalising theories of these conditions (Abu-Akel and Bailey 2000; Frith 2004), although it should be noted that increased activity in a mentalising region does not necessarily equate to hypermentalisation per se. For example it may mean that a region has to generate more activity to accomplish a typical degree, or even a reduced degree, of mentalising.

Increased activity in the temporoparietal junction has been reported in people with schizophrenia compared to controls when making judgements of a non-social, but not a social, nature (Bara, Ciaramidaro et al. 2011) which the authors interpret as indicating that people with schizophrenia are inappropriately reading intentions into non-intentional stimuli, an idea similar to that of Blakemore et al (2003). The findings of the current study, suggest that in people with SPD, this over-mentalisation is limited to explicit

social judgments, as opposed to being 'inappropriately switched-on' at other times as has been reported for schizophrenia. This in turn may represent a correlate of the mechanism by which individuals with SPD are spared the more severe symptomatology associated with schizophrenia. A direct comparison between schizophrenia and SPD would help to confirm or refute this hypothesis.

The decrease in activation in the posterior cerebellum seen between the ASD and SPD groups are also seen, but to a lesser extent, in the ASD versus CM and ASD versus control comparisons, indicating that function in this region is particularly affected in ASD. Although classically associated with motor co-ordination, the cerebellum, particularly the posterior aspect, has been found to be activated during a wide variety of cognitive and emotional fMRI tasks (Stoodley and Schmahmann 2009; Keren-Happuch, Chen et al. 2012). As well as the fMRI evidence, patients with known organic lesions of the cerebellum, either through stroke (Roldan Gerschcovich, Cerquetti et al. 2011) or spinocerebellar ataxia (Garrard, Martin et al. 2008) have been reported to show impairments in mentalising. The cerebellum was one of the earliest sites identified as abnormal in ASD in both post-mortem (Bauman and Kemper 1985) and structural MRI studies (Courchesne, Yeung-Courchesne et al. 1988). fMRI studies in ASD have also identified differences in cerebellar function compared to controls, including in tasks of social cognition (Critchley, Daly et al. 2000; Deeley, Daly et al. 2007; Herrington, Baron-Cohen et al. 2007; Silani, Bird et al. 2008; Grèzes, Wicker et al. 2009).

In the clusters where the ASD and SPD groups differed, the CM group tended to show increases in activation which were similar to the SPD group, as opposed to the decreases which were seen in the ASD group (Figures 5.11 – 5.12). This could suggest that the CM group are in fact similar to the SPD group, as opposed to being truly comorbid for both ASD and SPD. However, there were also differences found between the CM and the ASD in the cerebellum and the around the central sulcus, and between the CM and SPD group in the prefrontal cortex. The cerebellar cluster identified is similar to that observed in other comparisons and reflects a consistent decrease in cerebellar activation in the ASD group compared to all the other groups. However, with respect to the two frontal clusters the CM group are quite different from both the ASD and SPD groups, suggesting that these represent aberrances in brain function which are unique to this group. This is supported by the symptom – difference value correlations for the central sulcus cluster where the CM group show quite different relationships from the other groups (Figure 5.17). One possible interpretation of these findings is that individuals who meet criteria for both ASD and SPD have neither one disorder or the other, nor do they simply have the features of both. It is possible that the combination of the two disorders is additive such that less pronounced brain activation differences become more apparent when the two are combined. Alternatively it may be that the CM group are also affected by an additional factor (or factors) associated with frontal lobe dysfunction. However, the small number of participants in the CM group prevents any firm conclusions from being drawn.

The current study provides little evidence to suggest that specific clinical dimensions are related to different underlying mechanisms in people with ASD compared to those with SPD. None of the clusters which differed significantly between the ASD and SPD groups showed interactions between activation and group membership on the degree of either autistic or schizotypal traits. There was some suggestion that negative schizotypal traits showed a negative association with activation in the central sulcus cluster defined from the ASD<CM contrast in the SPD group but not the ASD group, but the significance of this interaction was driven more by the difference between the SPD and CM group than that between the ASD and SPD groups. It should be noted however, that the current design matrix was not set up to specifically explore symptom effects and it is possible that differences between the groups in activation-symptom relationships exist outwith the regions which differed significantly between the groups.

N-back task

When all the groups were considered together significant increases in activation were seen as WM load increased in the dorsolateral and dorsomedial frontal regions, parietal lobes, basal ganglia and cerebellum. These findings are broadly in line with those of the meta-analysis of Owen et al (2005) which primarily identified frontoparietal regions to be involved in working memory. Decreases in activation were seen throughout the cingulate gyrus, in the pre- and post-central gyri, insula, and temporal regions. Again these are broadly consistent with previous studies of task related activations (Tomasi, Ernst et al. 2006) and include many regions commonly held to be part of the network of brain

regions which are active at rest, the default mode network (Buckner, Andrews-Hanna et al. 2008).

The within group maps showed activation of similar regions to those outlined above. The ASD, SPD and especially the CM groups appeared to activate these regions less extensively than the controls. Deactivations appeared broadly similar in the ASD, SPD and control groups; the CM group showed no significant areas of deactivation. When the parametric contrast to examine increasing WM load was employed, compared to the controls, the ASD group showed a significantly smaller increase in activation (or a larger decrease in activation) in the left lateral parietal lobe stretching into the occipital lobe; whereas the SPD group showed a significantly smaller increase in activation (or a larger decrease in activation) in the posterior medial parietal and occipital regions bilaterally. No significant differences were seen between the CM group and the controls, or between any of the ASD, SPD and CM groups.

The lack of a difference between the ASD and the SPD groups is in contrast to the original hypothesis that the groups would differ with respect to the compensatory mechanisms employed to carry out the n-back task successfully. Although the ASD and SPD groups showed slightly different changes in activation as WM load increased compared to controls (see below), these did not differ significantly between the groups and inspection of the plots of the extracted values indicates that no difference is likely. In addition, activation within these regions did not relate to performance on the task suggesting that they are not compensatory in nature. It therefore appears that individuals

with ASD and those with SPD cannot be separated with regard to the brain activation associated with working memory, be it compensatory or deficit related.

Comparing the within group activation map for the ASD and the control groups (Figures 5.20 and 5.21) shows that both groups significantly activate the left lateral parietal lobe as WM load increases. The difference between the groups in the direct contrast likely represents a failure to activate this region in response to increased WM load in the ASD group. This is in contrast to the prediction that people with ASD would show greater activation of posterior brain regions to compensate for hypofrontality, indicative of a visual processing style. Instead the findings of the current study suggest that individuals with ASD show a relative failure to recruit the parietal lobe as WM load increases in the presence of preserved frontal lobe function. It is possible that this relates to reductions in long range connectivity which have previously been described in ASD (Philip, Dauvermann et al. 2012).

When the within group maps for the SPD and control groups are compared, it is apparent that both show decreases in activation in the medial parietal lobe as WM load increases. Thus, the difference between the groups identified in the direct contrast is likely due to greater deactivation of the posterior medial parietal lobe in the SPD group. The posterior medial parietal lobe is well established as forming part of the default mode network (Buckner, Andrews-Hanna et al. 2008). This is a network of brain regions which are known to be active at rest and hypothesised to relate to monitoring of the environment (Hahn, Ross et al. 2007) and / or self-reflective thought (Buckner, Andrews-Hanna et al.

2008). The latter in particular concerns socially mediated judgements which are known to involve many of the medial brain regions involved in the default mode network. Individuals with SPD therefore show a greater deactivation of one component of the default mode network, which may reflect higher baseline activity in this region. Consistent with this, increased connectivity of the default mode network at rest has been previously reported in people with schizophrenia (Broyd, Demanuele et al. 2009). The current findings suggest that this too may be the case in SPD and are consistent with the idea that schizophrenia spectrum disorders are associated with aberrant self-monitoring and hypermentalisation (Frith 1992; Abu-Akel and Bailey 2000; Frith 2004). This interpretation is further supported by the significant relationship seen in the SPD group between positive schizotypal traits and increasing deactivation of this region (Figure 5.28). It should however be noted that the contrast used in the current study is of changes in activation as working memory load increased from the 1-back condition to the 3-back condition. Thus the potential over-activation at baseline in fact represents an over-activation during the 1-back task, as opposed to in a true resting state, and a greater deactivation in this region under the 3-back condition. That this finding did not relate to task performance suggests that this change is not simply due to failure to complete the task, rather it may relate to an inappropriate persistence of baseline overactivation in the easier working memory task, which cannot be maintained as working memory load increases. The inclusion of a baseline rest component to the n-back task would have allowed this issue to be teased apart more fully.

It is interesting to note that the relationship between the deactivation described above and positive schizotypal traits differs between the CM and other groups, particularly the CM and SPD groups. This is consistent with the findings for the symptom-activation relationships reported for the social judgement task and provide further preliminary evidence that the CM group differ from both the ASD and SPD groups.

Conclusion

Despite similar behavioural performance, significant differences in activation were seen in social brain regions when individuals with ASD and SPD were asked to make a social judgement. Individuals with SPD over-activated such regions compared to those with ASD who showed reduced activation, with the controls tending to sit midway between the two. These findings are consistent with the idea that SPD is associated with hypermentalising and ASD is associated with hypomentalising. In contrast, no differences were found between the groups with respect to brain activation during a working memory task suggesting that the differences between the groups may be primarily related to social cognitive processes, as opposed to executive function. Individuals who meet criteria for both disorders, may have additional factors which account for their difficulties, over and above those associated with either of the single disorders alone.

Chapter 6

Summary discussion and future directions

6.1: Findings of the current study

This is the first study to comprehensively compare ASD and SPD across a range of features derived from clinical, neuropsychological and functional brain imaging investigations. In the clinical study it was found that it was possible to clinically distinguish individuals with ASD and SPD in most cases, although just under 20% of participants met criteria for both conditions and these individuals were more severely affected across multiple clinical domains than either condition alone. Even when a single diagnosis could be made, there were clear overlaps of clinical features and each condition showed more traits of the other than were seen in controls. The overlaps were most prominent for negative schizotypal traits which did not differ between the groups. The degree of similarity between the disorders was even more striking in the neuropsychological study. Both showed similar evidence of impairment in social cognitive and executive function tasks, with only minimal differences seen in local-global processing (and these were potentially confounded by IQ). The fMRI study was more revealing of differences between the groups with respect to social cognition. Despite similar behavioural performance on the social judgement task there were clear activation differences seen between the ASD and SPD groups in social brain regions and the cerebellum. Differences also existed between the CM and the ASD and SPD groups suggesting that this condition represent more than the simple addition of ASD and SPD. When activations during a working memory task were considered there were no significant differences between the ASD, SPD and CM groups. Correlations of the clinical measures with the neuropsychological and fMRI measures that differed between

the groups did not convincingly reveal any clear differences between them with regard to the mechanisms by which their symptomatology might develop.

6.2: What do the findings tell us about the relationship between ASD and SPD?

As reviewed in the introduction to Chapter 2, two major theories have been advanced to conceptualise the relationship between the autism and schizophrenia spectrums. The first is that the two conditions are diametrically opposed disorders which result from sexually dimorphic genomic imprinting (Crespi and Badcock 2008). The second hypothesis is that autism and schizophrenia are related disorders, occupying two points on a broad spectrum of neurodevelopmental disorders (Carroll and Owen 2009; Craddock and Owen 2010; Cross-Disorder Group of the Psychiatric Genomics, Smoller et al. 2013).

The findings from the neuroimaging study could be used to support either of these positions; the 'double dissociation' of brain activations shown in the social judgement task is consistent with the idea that the conditions are diametrically opposed, whereas the lack of significant differences in the fMRI of the n-back task is consistent with the idea that the two are related disorders. However, the results from the clinical and neuropsychological components of the current investigation are more in keeping with the idea that ASD and SPD are related disorders which show partial overlap. Further evidence for this comes from the lack of convincing evidence that different brain mechanisms are associated with the overlapping clinical features of the conditions. If they were indeed fundamentally opposed as suggested by Crespi and Badcock (2008) one would expect that those features which looked similar would show quite distinct

associations with brain function. This was not observed within the context of the current study. Finally, that a significant proportion of individuals exist who meet criteria for both conditions is difficult to equate with the idea that the two disorders are in opposition to each other.

Although the overall evidence from the current study suggests that there is a partial overlap between the autism and schizophrenia spectrums, the clearest positive findings were that the two conditions show opposing mechanisms with respect to their mentalising impairments. This would suggest that, in this aspect at least, the disorders are distinct. Although there is considered to be genetic overlap between autism and schizophrenia (Cross-Disorder Group of the Psychiatric Genomics, Smoller et al. 2013), there are also many genes which are thought to be associated with one condition and not the other (Crespi, Stead et al. 2010). The effect of the genetic factors which are not shared between the conditions may be such as to produce this double dissociation in social brain function, either independently or through their interaction with shared genetic factors. Alternatively, it is possible that differences between the conditions in spatiotemporal gene expression, epigenetic factors or gene-environment interactions may be responsible for the apparently opposing brain activity described.

More broadly speaking, it is apparent from the historical review in Chapter 1 that the diagnoses of ASD and SPD have been derived from observed clinical phenomena in individuals affected by these conditions and / or their relatives. There has been no particular framework used to drive their derivation (in common with other aspects of

psychiatric classification) and they have arisen largely from different traditions (for example, ASD has arisen from behavioural observations made in child psychiatry, whereas SPD focuses more upon cognitive symptoms from an adult psychiatric tradition). The findings from the current study suggest the possibility that mentalising style may be one way in which an overarching cognitive framework could be used to inform future classification. This is in keeping with the Research Domain Criteria initiative by the National Institute of Mental Health in the USA, which proposes giving up conventional psychiatric diagnosis and focusing on domains of function developed from social, biological and cognitive science. It would be appealing to recruit a group of individuals with multiple different psychiatric diagnoses relating to social dysfunction (e.g. avoidant personality disorder, SPD, ASD, social phobia) and examine whether individuals could be categorised into hypo- and hyper-mentalising. If this were possible one could then consider whether these groups determined on mentalising style clustered on other clinical and biological features, and on response to specific treatments.

6.4: What are the practical implications of the current study?

The study carries a number of implications for clinical practice. Perhaps the most immediate is that clinicians should be alert to the possibility that individuals with one condition may also meet criteria for the other and that people who are thus affected show particularly high levels of psychiatric morbidity across multiple domains. Indeed, the high levels of psychiatric disorder identified in all of the clinical groups stands in contrast to the relatively low self-reporting of previous mental disorder diagnoses, suggesting that these groups suffer unnecessary distress from untreated psychiatric disorder. Less

immediately, the differences between the groups in the social brain activity associated with mentalising impairments suggest that treatments directed at improving social dysfunction need to be appropriately tailored to each group.

Outwith clinical practice the relatively high co-occurrence of ASD and SPD has important implications for academic research studies directed at elucidating aetiological or pathophysiological factors of these conditions. This is particularly important given those who met criteria for both disorders show differences in brain activity than were seen for either disorder alone. Although many studies of ASD will exclude individuals who have an Axis I psychiatric disorder, to the author's knowledge none consider the presence of SPD as an exclusion criterion. Similarly, again to the best of the author's knowledge, no studies of SPD have examined for the presence of ASD in their sample. The findings of the present study suggest that without considering these as exclusion criteria, such samples are likely to have increased heterogeneity and subsequently reduced power to find true positive results.

6.5: Methodological issues

There are a number of methodological issues in the current study which deserve comment. Firstly, the sample size is relatively small, particularly for the comorbid group, meaning that the degree of confidence in negative results in particular is limited. A larger sample of participants may have identified more subtle but important differences between the groups. The recruitment of individuals who have conditions associated with social withdrawal and paranoid ideation is difficult, particularly for such a detailed

investigation. This is highlighted by the fact that although relatively small, the current study is the largest fMRI study ever conducted in SPD and one of the largest for ASD.

Like most research studies, the sample recruited may not be representative of the generality of people with ASD and SPD. The limitation to relatively high IQ individuals means that it is not possible to extend the findings to the approximately 50-70% of people with ASD who also have intellectual disability (Matson and Shoemaker 2009). However, this was necessary in order to provide a fair comparison to people with SPD, the majority of whom are not known to be intellectually disabled. In addition, the samples were recruited from several different sources, with the major difference being that all individuals with ASD had been diagnosed by a specialist diagnostic service, whereas those with SPD were mainly derived from a previous research sample and had not been in contact with clinical services. Thus the ASD sample may represent a relatively more affected group with this condition than the SPD sample. However, the median score on the ADOS was 7 which is the lower limit of the cut-off for ASD on this instrument, suggesting that the current sample of people with ASD was actually a relatively mildly affected one. It is also important to note that many of the participants, including the entire CM group, had a history of psychiatric disorder which may have affected the results. In part this may relate to the fact that the ASD group were recruited from a clinical service, although this was not the case for the SPD group who also showed high levels of comorbid psychiatric disorder. Differences between the groups in terms of psychiatric history may have confounded the differences reported. However, to exclude such individuals would result in a skewed sample, unrepresentative of the broader population

of individuals affected by these conditions.   Finally, with regard to subject selection, individuals who volunteer to take part in research are a self-selecting group and one obvious way this was reflected was in the above-average IQ of the sample.   Less obviously, but perhaps more importantly, individuals who were more socially withdrawn or with higher levels of persecutory ideation are not likely to volunteer for such studies

From a methodological perspective, the most obvious weakness of the current study was that, outwith the fMRI analysis, multiple comparisons were not corrected for, therefore at least some of the findings reported in this thesis are likely to have resulted from Type II error, particularly those which were unexpected.   Replication of the current findings is therefore essential.   A second potential weakness is the lack of use of a standardised developmental history in making the diagnosis.   The inclusion of such a history may have provided information particularly pertinent to the classification of the CM group.   The ADI-R was used to investigate for potential developmental differences between ASD and SPD but was not included as a diagnostic measure for two reasons: firstly, it is difficult to obtain such a history for many adults with ASD therefore the current study is perhaps more reflective of clinical reality; secondly, although it is considered as a gold-standard diagnostic measure for autism the ADI-R has not been validated for consideration of the broader autism spectrum and therefore was not suitable for the purposes of the current investigation.

6.6: Future directions

In this, as with any, large dataset there are many analyses over and above the ones presented here which can be conducted to further understand the conditions. Dysconnectivity has been suggested to be important in both ASD (Müller, Shih et al. 2011; Just, Keller et al. 2012) and SPD (Hazlett, Goldstein et al. 2012) therefore conducting connectivity analyses of the fMRI data may shed further light on the findings reported here and perhaps reveal further differences between the groups. Similarly analysis of the structural MRI data which were also collected for the current study may provide further information about the relationship between ASD and SPD. Whether specific symptom dimensions which overlap between the groups are associated with differing underlying mechanisms could also be investigated more precisely using a different statistical design which includes the symptom in question as a covariate and a group x symptom interaction term. In this regard the differences in symptom correlation measures which were identified in Chapter 3 should be probed further by looking at more precise symptoms, i.e. individual positive or disorganised symptoms, as opposed to considering them as groups of symptoms.

Future studies should examine the hypo- versus hyper-mentalising theory of the autism and schizophrenia spectrums in more detail. Hypomentalising is construed as the under-ascription of mental states to stimuli when such ascriptions would be appropriate; hypermentalising therefore represents the inappropriate over-ascription of mental states to stimuli. The social judgement task, as analysed in the current study, considers only explicit social reasoning, which covers only one possible aspects of hypo- and hyper-

mentalising. Clearly clinical difficulties exist in ASD and SPD which go beyond what would be expected if only explicit mentalising was affected; therefore consideration needs to be given to whether ASD and SPD also differ through opposing implicit mentalising styles. In the past, groups have examined implicit mentalising through the use of apparently non-social stimuli, such as moving triangles and shapes. In such tasks the viewer tends to ascribe social actions to the shapes if their movements are anthropomorphised (Castelli, Happé et al. 2000; Blakemore, Boyer et al. 2003). If hypermentalisaion exists in a clinical group such tasks should overactivate social brain regions compared to controls, similarly hypomentalisaion may be revealed as underactivation. However, the use of such tasks in individuals with ASD may be inappropriate as differences in implict ascription of mental states to non-social objects could result from concrete or literal thinking as opposed to hypo-mentalisation *per se*, i.e. an individual with ASD may not view shapes as being anything other than shapes which is quite different from not implicitly ascribing mental states to a stimulus. It would perhaps be more useful to construct a study where a real social stimulus is used but which can contain varying degrees of cues designed to provoke implicit mentalising by, for example, varying the degree to which people are seen to be interacting.

In regard to the other domains of cognitive function tested, the current study found few differences between the groups, which is somewhat surprising given that the tasks were specifically chosen as they were hypothesised to discriminate the groups. Although this may reflect a genuine lack of a difference between the groups or a lack of statistical power, it may also indicate that the specific tests chosen were not sensitive enough to

tease out more subtle differences between the groups. More detailed investigation of the local versus global processing bias may be informative, as the current study did not consider tasks which fractionate the two processes. The lack of a difference between the groups, even from controls, was particularly striking for the executive function tests. More fine grained analysis of executive function may be warranted in the future to determine whether there is a true lack of executive deficit. For example, considering several different types of working memory, as opposed to just verbal, and using a more difficult continuous performance task than the SART might be beneficial. However, executive dysfunction is present in many different psychiatric disorders and it may be unrealistic to expect that either ASD or SPD would show specific deficits not seen in the other.

The differences between the groups in positive and disorganised symptom correlations with autistic traits merit further study to clarify what they represent. The basis of psychiatric classification relies upon grouping constellations of symptoms into syndromes; this carries the implicit assumption that the symptoms within a syndrome have some form of shared aetiology and / or pathophysiology. The differences between ASD and SPD identified in the current study imply that these symptoms do not cluster in the same way in the groups. The imaging findings from the current study suggest that at a pathohysiological level there are differences between the groups which implies that this difference in clustering may relate to the fact that these symptoms are not the same. If true, this would mean that the rating scales used to identify symptoms are not sensitive enough to discern differences between them. Alternatively, it may be that the genetic or

environmental disturbances associated with the development of ASD or SPD overlap only insomuch as those factors which are associated with negative symptoms. It would be instructive to design an experiment to consider the potentially shared aetiological factors and their relationship with symptoms in each group. Indeed, determining the relationship between identified deficits in all domains and potential aetiological factors would also help to establish whether shared or distinct genetic characteristics are associated with, for example, the mentalising impairments in the groups.

Finally, the potential relevance of the current work to research into therapeutic interventions for ASD and SPD should be considered. Psychological treatment programmes targeted at social deficits in the autism and schizophrenia spectrums should be targeted towards the correction of hypo- and hypermentalising respectively. In addition, there is currently great interest in the development of potential medications to treat the social deficits of autism (Ecker, Spooren et al. 2012; Murphy and Spooren 2012; Farmer, Thurm et al. 2013; Tachibana, Kagitani-Shimono et al. 2013) and the negative symptoms of schizophrenia (Hashimoto, Malchow et al. 2013; Miyamoto, Jarskog et al. 2013) . Identification of whether an affected individual has a hypo- or a hyper-mentalising style may be a useful predictor of response to such treatments.

6.6: Conclusions

It has been over one hundred years since the word autism was first used by Bleuler in the context of schizophrenia, and more than sixty years since it became a disorder in its own right. In this time, marked changes to the concepts of both autism and schizophrenia

spectrums have occurred, such that spectrum forms of the conditions are now well recognised and catered for within structured classificatory systems. However, the relationship between these spectrums has never been clearly established and diagnostic separation is difficult. The current study revealed that substantial overlaps occur between the conditions, with regard to both clinical and neuropsychological measures. However, a clear dissociation between the disorders was seen in terms of the brain function associated with deficits in understanding the mental states of others. Thus, the autism and schizophrenia spectrums, while likely to be partially overlapping, show clear differences in relation to one of their cardinal symptoms such that ASD and SPD are therefore correctly regarded as separate disorders.

Chapter 7

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